DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR FISCAL YEAR 2014

WEDNESDAY, APRIL 2, 2014

U.S. SENATE,
SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 10 a.m., in room SD–192, Dirksen Senate Office Building, Hon. Tom Harkin (chairman) presiding.

Present: Senators Harkin, Durbin, Mikulski, Moran, Cochran, Shelby, and Kirk.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF FRANCIS S. COLLINS, M.D., PH.D., DIRECTOR

ACCOMPANIED BY:

ANTHONY S. FAUCI, M.D., DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

HAROLD E. VARMUS, M.D., DIRECTOR, NATIONAL CANCER INSTITUTE

GARY H. GIBBONS, M.D., DIRECTOR, NATIONAL HEART, LUNG AND BLOOD INSTITUTE

STORY C. LANDIS, PH.D., DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

CHRISTOPHER P. AUSTIN, M.D., DIRECTOR, NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. The Appropriations Subcommittee on Labor, Health and Human Services, and Education, and Related Agencies will come to order. Good morning, everyone, and welcome. Sorry we are a little late. We had a vote at 10—that is all.

Well, today will be my final Appropriations budget hearing for the NIH (National Institutes of Health) as the chair of this subcommittee. I took over this subcommittee from Senator Lawton Chiles in 1989. That is a long time ago it seems, a quarter century. I am so proud of all that we have done—all of us here—often on a bipartisan basis, to transform the National Institutes of Health into truly the jewel and the crown of biomedical research not only in the United States, but globally.

On Tuesday, as many of you know, I was on the NIH campus to help dedicate the new John Porter Neurosciences building. I was struck as I drove around the campus by the growth and modernization that has taken place there in the last 25 years. But that physical transformation has been more than matched by the transformational science and discovery that has sprung from that campus.

If you do not mind, a little bit of reminiscences. My first year as chair was the first year that we invested NIH dollars in an exciting new project to map the human genome, 1989. I will never forget. I had taken over this subcommittee and I was visited by Dr. James Watson, whom I had never met before, but of course I had read about him—the famous Nobel Prize winner—Watson and Crick, discoverers of the double helix. And so, I was quite full of myself when as a freshman Senator I was visited by this great scientist who wanted to talk to me about investing in mapping and sequencing the human gene. I had no idea what he was even talking about at that time, but he brought me along a little bit, and so we were able to put a little bit of money into that.

Thanks again to all that initial work. And thanks to the work of Dr. Collins and his colleagues at NIH. We can now sequence the human genome at a fraction of the cost that it required, and in a shorter timeframe. I might just add, there was a study done by the Battelle Institute. It came out last year and said that the U.S. Federal Government's $3.8 billion funding of the Human Genome Project between 1988—actually it's 1989, but that is okay—between 1988 and 2003 drove $796 billion in U.S. economic impact due to the growth of the genomics technology industry and the use of genomics in healthcare, energy, agriculture, and other sectors—quite a rate of return on investment.

And consider this: In 1989—I remember it well in the 1980s—HIV (human immunodeficiency virus) was a death sentence. Today, thanks in large part to the leadership of Dr. Anthony Fauci, HIV is a manageable chronic disease, and we know how to prevent it. Since 1989, the proportion of older people with chronic disabilities has dropped by nearly one-third. Cancer death rates in the U.S. are now falling at a rate of nearly 1 percent each year. And each 1-percent decline saves our Nation nearly $500 billion. There has been near miraculous progress in the fight against childhood cancers with the 5-year survival rate for the most common type, acute lymphocytic leukemia, now rising to a 90-percent cure rate. That is fantastic.

Two of our witnesses here today direct centers that did not exist, that were not part of NIH in 1989. The National Institute of Mental Health moved from SAMHSA (Substance Abuse and Mental Health Services Administration) to NIH in 1992, and this subcommittee created the National Center for Advancing Translational Sciences (NCATS) in 2011. And although the directors are not here today, I am particularly proud to have authored the bill that created the National Institute on Deafness and Communication Disorders in 1988. Again, as I said, we worked to elevate the Genome Research Office at that time to a center in 1989, and we created the National Center for Complementary and Alternative Medicine in fiscal year 1992. Looking back to 1989, my notes tell me that

in 1989 a Yale scientist named Francis Collins led a research team to discover the gene for cystic fibrosis.

How far the NIH has come in 25 years. So many Nobel Prizes. So many life-saving discoveries. This subcommittee has had no higher priority than to support NIH and the scientists all across America dedicated to reducing suffering and improving public health. So this is a bittersweet moment for me and for all of us who revere the work of NIH because these great achievements are in the past. The future leadership of NIH is threatened by penny wise, pound foolish thinking by too many here in the Congress. Most in Congress are obsessed by budget deficits. I am more concerned by our deficits of vision and ambition and leadership.

I am proud to say that since 1989, I have either chaired or been the ranking member of this subcommittee. Most of that time with Senator Arlen Specter. We kept changing back and forth as the leadership of the Senate would change, more recently with both Senator Shelby and now Senator Moran on this committee. So it has been, for me, an enlightening experience, through all these years. I do not have a science background, a bit of an engineering background, but not much of science. So for me it has just been eye opening to see what has happened with NIH through all these years.

As our Government charts a course of stagnation and disinvestment in biomedical research, other countries are surging ahead. China's government pledged to increase its basic research investment by a staggering 26 percent just in the last year and will invest more than $300 billion in biotechnology over the next 5 years, twice what we are planning on doing.

So this is the context in which we consider the proposed funding levels for fiscal year 2015. The Murray-Ryan budget deal partially replaced the sequester for the coming year, and while I am pleased that the subcommittee has a solid top line figure to work with, these austere budget caps are wreaking havoc on NIH and other national priorities.

With a non-defense cap that increases by $583 million this year, it is mathematically impossible to fully replace the remaining NIH sequester and provide just an inflationary increase to NIH without forcing additional cuts to education, and job training, and other priorities.

By not replacing the sequester this year, we are foregoing $56 billion that could be invested in programs to grow our economy, programs like NIH. The President proposed a fully offset opportunity growth and security initiative that represents the $56 billion in lost—that was lost to sequester. That initiative would allow for investing an additional $900 million in NIH, enough to bring NIH back to the pre-sequester level and then provide a small increase. That is what we are losing by clinging to this devastating policy of sequester. Make no mistake: Keeping the sequester in place will mean a steady, destructive erosion in our NIH investment. It is no longer a question of politics; it is just a question of math.

So I look forward to the discussion today about the exciting work that NIH is doing in the face of these budget problems, and in the hopes that we can all work together to support this vital institution, and to maintain America's leadership in our biomedical

sciences. With that, I will yield to Senator Moran for his opening statement.

STATEMENT OF SENATOR JERRY MORAN

Senator MORAN. Mr. Chairman, thank you. I look forward to continuing to work with you during the remainder of your term as chairman of this subcommittee along with Senator Shelby, the ranking member, and Chairwoman Mikulski to see that we accomplish some of the goals that you outlined in your statement.

And I do appreciate Dr. Collins and his colleagues being with us today to discuss the National Institutes of Health. In my view, NIH represents hope for millions of patients suffering from conditions from Alzheimer's disease to cancer. NIH-funded research has raised life expectancy, improved the quality of life, and is an economic engine helping to sustain America's competitiveness.

Over the past year, cutting-edge NIH-supported research discovered a blood test to predict if a healthy person will develop dementia or Alzheimer's disease, uncovered a set of rare mutations to a gene that provides protection against type 2 diabetes, and used targeted immunotherapy to induce remission in leukemia. What wonderful developments. A continued commitment to NIH is essential to address our Nation's growing health concerns, spur medical innovation, sustain American competitiveness, and reduce healthcare costs.

I think NIH is at a critical juncture. We have spent years focusing on doubling the NIH budget, and now a decade later the NIH budget is falling victim to an Administration's budget that does not prioritize biomedical research. The fiscal year 2015 budget touts an increase of $200 million, or 0.7 percent, seven-tenths of a percent. However, with the use of, really, a budget gimmick, the increase is all but eliminated with the President's proposal to increase the evaluation set-aside. Under the President's proposal, $142 million of the $200 million increase would be transferred to other programs within the Department of Health and Human Services, leaving NIH with only a $58 million increase.

Without a consistent commitment to funding our premiere medical research agency, the future of biomedical research in the United States is in jeopardy. Grant success rates are at an all-time low. The average age of a first-time R01 grantee is 42 years old, up from 38 years old in 1980. I looked out across the list of the panel of witnesses and discovered that you all remain very young, so perhaps that is defeating the point I am trying to make. But our researchers are becoming older as we continue this process. In fact, our principal investigators who are 65 or older receive more than twice as many R01 grants than those 36 and under. Young scientists, which we desperately need, will be discouraged by these statistics, and many have fled research fields or left for opportunities in other countries, putting our Nation at a serious risk for losing our global competitiveness in the biomedical research field and reducing the chances that we find cures and treatments.

Dr. Collins has consistently raised this concern about what he calls "deep long-term damage" to biomedical research, and we should all pay attention to his warnings. We cannot let these research opportunities slip away. We cannot lose the brilliant sci-

entists, the scientific minds that will make future ground-breaking discoveries in biomedical research to alternative careers or other countries. And we must not squander the scientific capacity that we have developed.

I believe funding decisions represent more than just dollars. They reflect our Nation's priorities. And this Congress faces unprecedented challenges to reduce Government spending. Now is the time to reevaluate our funding priorities and invest after evaluating those priorities in biomedical research. This is the time of promise in research, and the United States should be at the forefront in this area. To do so, we must commit to pay for the research. We must accomplish this. And I thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Moran. Well, again, Dr. Collins and colleagues, welcome again to our subcommittee. I got your statement. I read it. It will be a part of the record in its entirety. And, Dr. Collins, we will recognize you. Just proceed as you so desire for 10 minutes or so, or whatever it takes you to get it done. Welcome back, Dr. Collins.

SUMMARY STATEMENT OF DR. FRANCIS S. COLLINS

Dr. COLLINS. Well, thank you, and good morning, Chairman Harkin, Ranking Member Moran, and members of the subcommittee. Let me introduce the folks at the table who are here with me: Over to your right, my left, Dr. Harold Varmus, the Director of the National Cancer Institute (NCI), formerly the director of the NIH; next to him, Dr. Gary Gibbons, Director of the National Heart, Lung, and Blood Institute; and immediately to my left, Dr. Christopher Austin, Director of the new National Center for Advancing Translational Sciences, NCATS; to my right, Dr. Story Landis, the Director of the National Institute of Neurological Disorders and Stroke; and finally as already mentioned, Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases. And they are here to answer your questions, as am I.

Well, it is a great honor for us to be here to appear before you and present the Administration's fiscal year 2015 budget request, and to provide an overview of our Agency's critical role in enhancing the Nation's health through scientific discovery. But before I begin today, I would be remiss if I did not take a moment to thank you, Mr. Chairman, for your extraordinary leadership on this subcommittee over these 25 years. You have been a remarkable—I would say even historic—advocate for biomedical research and for the NIH. We are all very grateful for your service, and will truly miss you on this subcommittee in the years to come.

[The graphic follows:]

NATIONAL INSTITUTES OF HEALTH MISSION

Dr. COLLINS. NIH has been advancing our understanding of health and disease for more than a century. Scientific and technological breakthroughs generated by NIH-supported research are behind many of the gains that you can see in this image of how our country has enjoyed gains in longevity and in health. For example, over the last 60 years, deaths from heart disease have fallen by more than 70 percent. Meanwhile, cancer death rates, as you have already cited, have been dropping about 1 percent annually for the last 15 years, life expectancy gains that have saved our Nation trillions of dollars. Likewise, HIV/AIDS treatments have greatly extended lives, and prevention strategies are enabling us to envision the first AIDS-free generation since this virus emerged more than 30 years ago.

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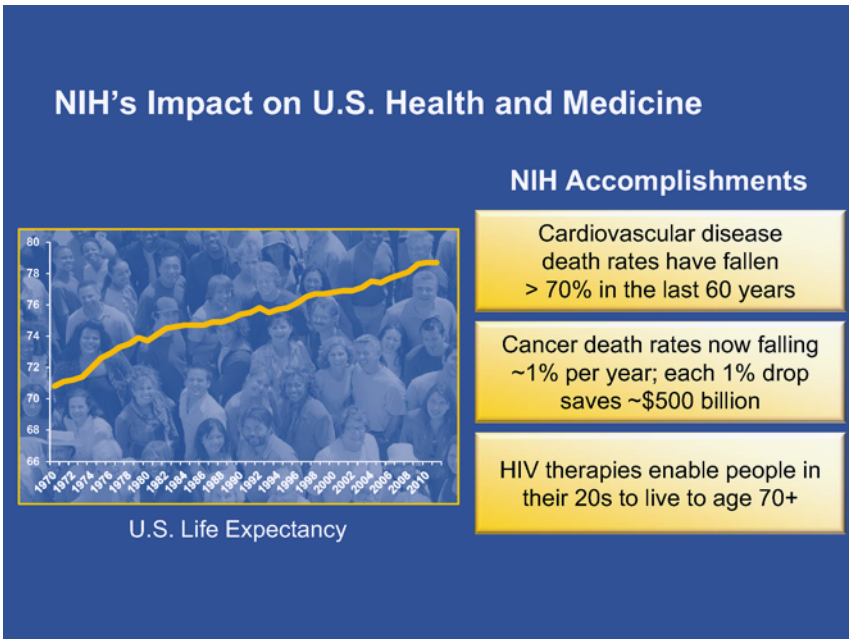

Dr. COLLINS. But none of these advances could have happened without the strong support of the Administration and the U.S. Congress, and specifically of this subcommittee. This subcommittee came together in a bipartisan way, and I want to thank you for that, to make it possible in the fiscal year 2014 omnibus appropriation to turn a corner.

BUDGET CHALLENGES

To be honest, the previous year was quite challenging for us. Sequestration applied damaging cuts to ground-breaking medical research and affected the morale of the scientific community. That impact was further exacerbated by the Government shutdown, which forced me to send 12,000 scientists home for 16 long days, and required us to turn patients away from the NIH Clinical Center.

With the fiscal year 2014 omnibus, we are optimistic that a corner has been turned after a difficult decade during which NIH has lost more than 20 percent of its purchasing power for medical research, 20 percent down from where we were in 2003. The Administration now proposes a fiscal year 2015 budget request that is $211 million, or .7 percent, above the fiscal year 2014 level. This budget request reflects the President's and the Secretary's commitment to improving the health of the Nation and to maintaining our leadership in the life sciences while remaining within the constraints of the Murray-Ryan budget envelope. It allocates resources to areas with the most extraordinary promise for medical research, while maintaining the flexibility to pursue unexpected scientific opportunities, and to address unforeseen public health needs.

Within the Administration's fiscal year 2015 budget, NIH will increase our primary funding mechanism for investigator-initiated research, the research project grants, or RPGs. And this is a critical priority. In fiscal year 2013, our grant success rate, as you can see in this graph, reached an all-time low of 16.8 percent, a number that desperately needs to rise again.

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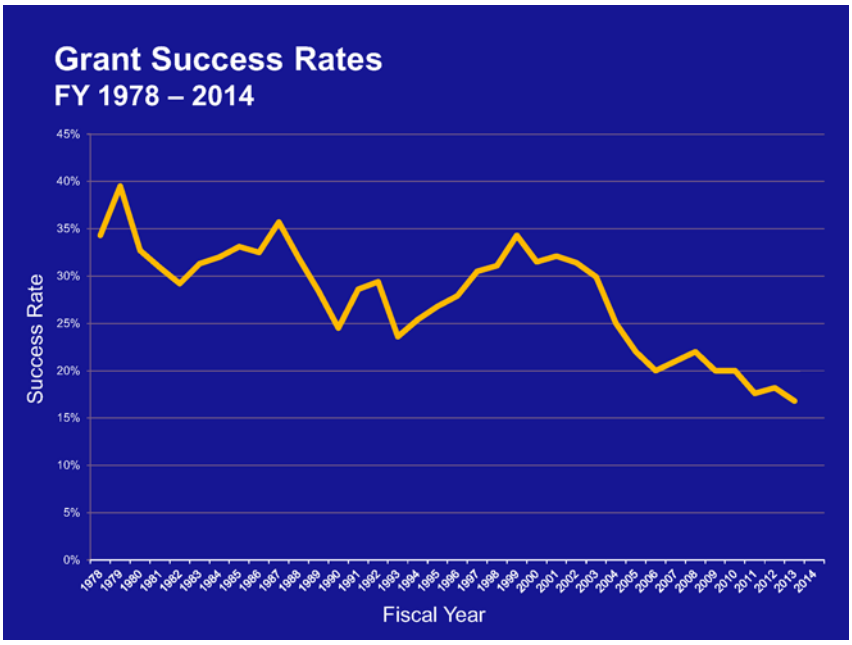
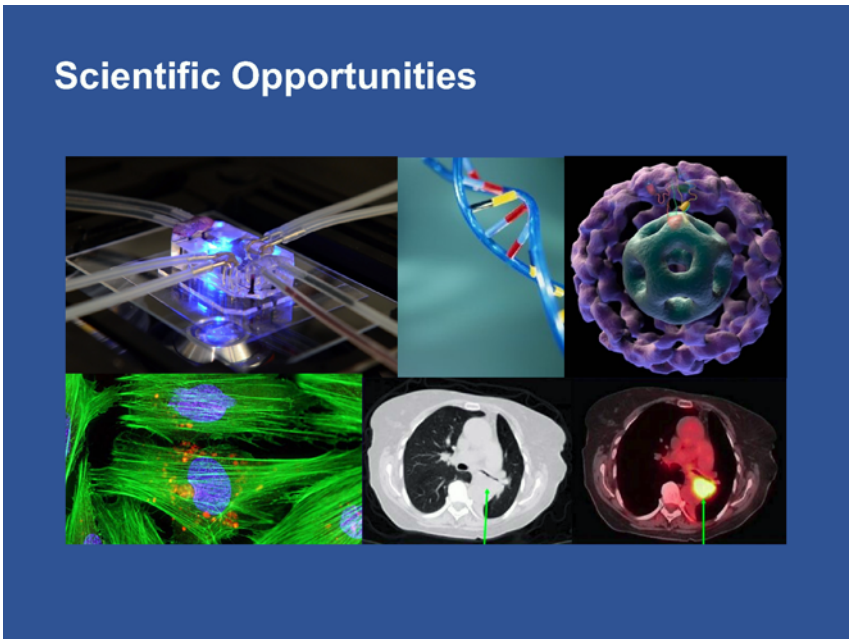


Dr. COLLINS. By careful stewardship of resources, we expect to support 9,326 new and competing RPGs next fiscal year, which will be an increase of 329 over fiscal year 2014 levels, although the total number of grants we support will remain approximately the same.

But now, let me turn to some of the exciting scientific opportunities that NIH is pursuing today.

[The graphic follows:]



FUTURE OF BIOMEDICAL RESEARCH

Dr. COLLINS. I can assure you the future of biomedical research has never been brighter. Basic science, for which the Federal Government serves as the main source of support in the U.S., had led the way. Advances in genomics, proteomics, stem cells, imagine, the microbiome, and other technologies have led to phenomenal advances in our understanding of how life works, and also the discovery of more than a thousand new risk factors for disease.

NIH will continue to spend a little more than half of our budget on these basic science advances. But as you know, we are also deeply committed to catalyzing the translation of these discoveries into clinical advances. And this can be quite challenging to the dismay of researchers, drug companies, and especially patients. We face a situation today where the vast majority of drugs entering the development pipeline fall by the wayside.

The most distressing failures, as you see here, occur when a drug is found to be ineffective in the later stages of development, in phase two or phase three clinical trials, after years of work and millions of dollars have already been spent.

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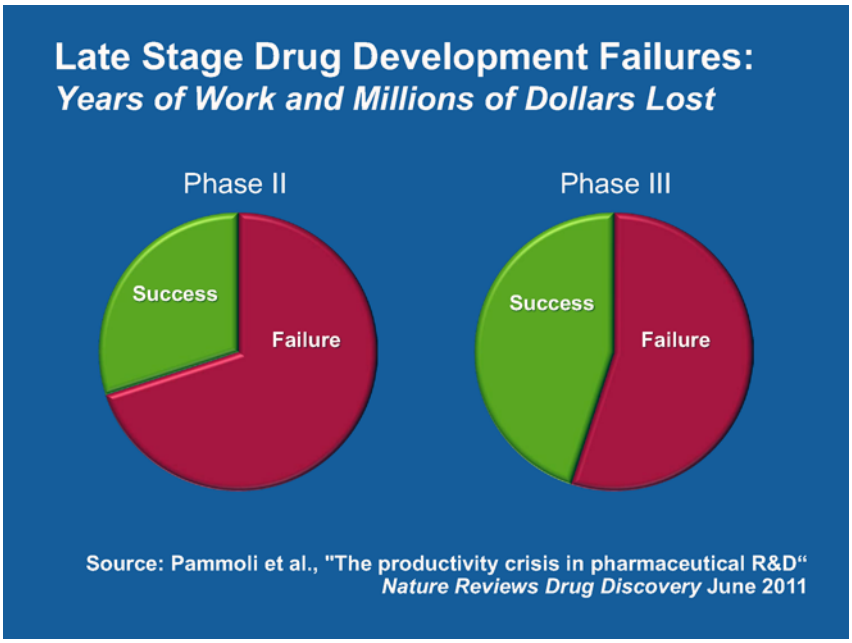

ACCELERATING MEDICINES PARTNERSHIP

Dr. COLLINS. A major reason for such failures is that scientists often have not had enough information to choose the right biological targets, and if a drug is aimed at the wrong target, it will not be effective against the disease it was intended to treat, and a failure will occur.

So to this end, we were particularly thrilled to announce the launch of the Accelerating Medicines Partnership, AMP, just 6 weeks ago.

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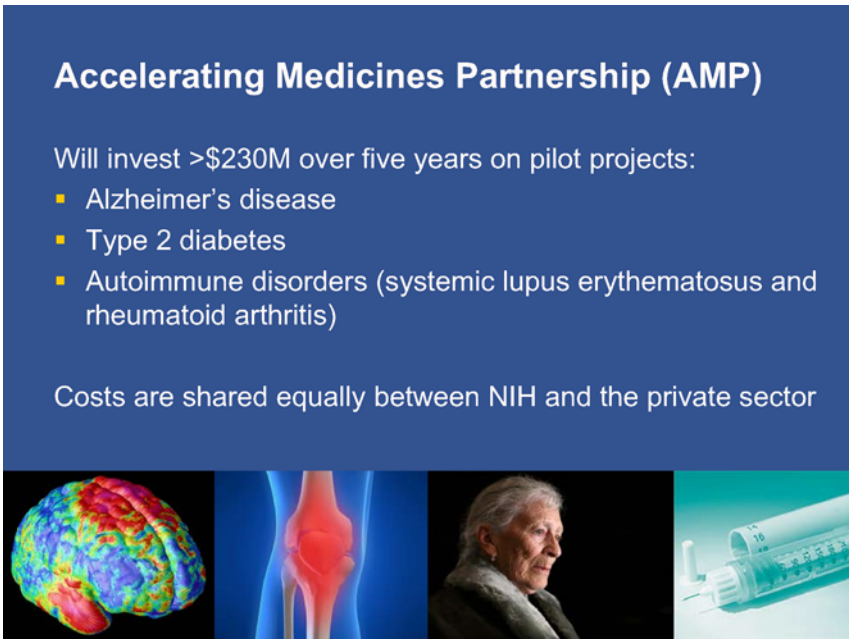

Dr. COLLINS. This pre-competitive partnership, which will share all data openly, will initially focus on three disease areas that are ripe for drug discovery: Alzheimer's disease, type 2 diabetes, and the autoimmune disorders lupus and rheumatoid arthritis.

Besides NIH, the partners in AMP include the FDA and 10 biopharmaceutical firms, listed here, and a number of non-profits, including patient advocacy groups.

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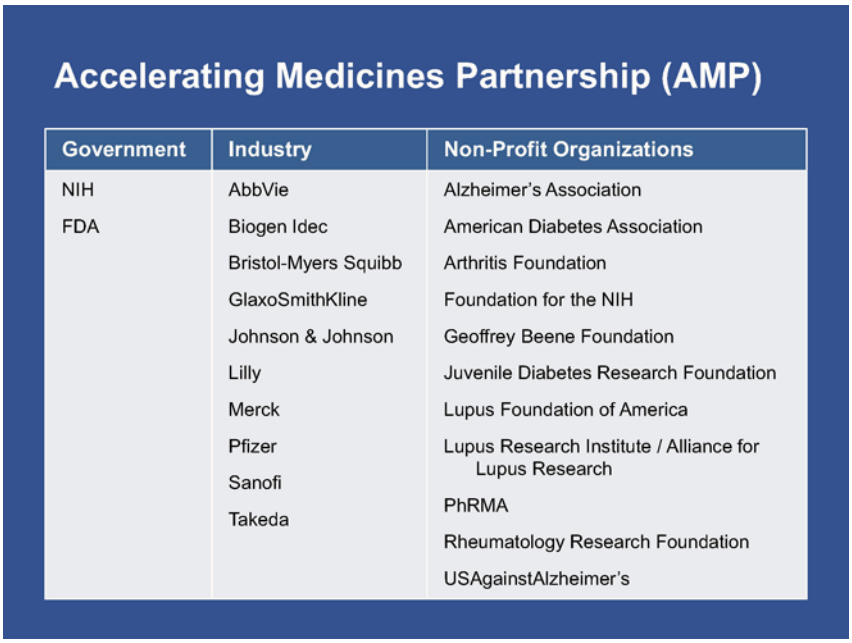
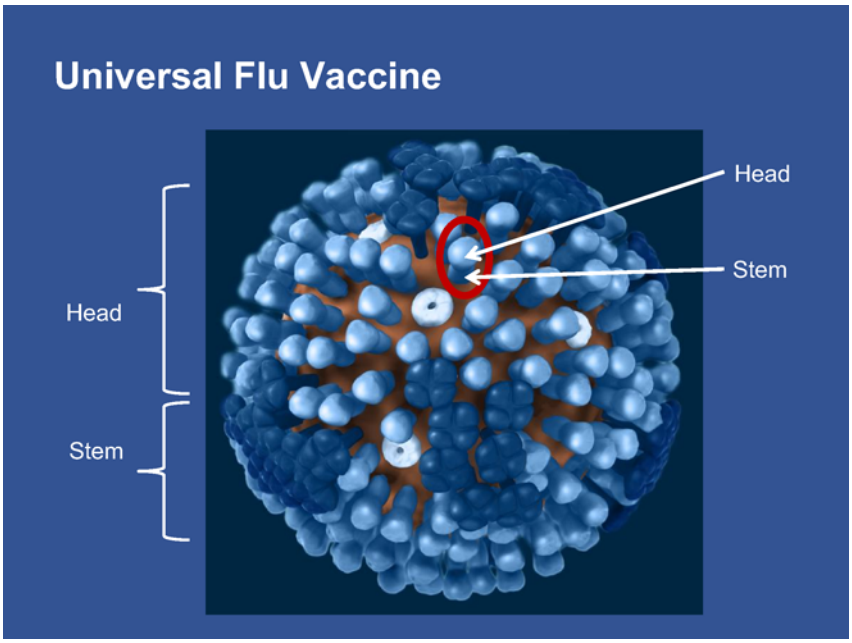


UNIVERSAL FLU VACCINE

Dr. COLLINS. This unprecedented public/private collaboration will use cutting-edge scientific approaches to sift through a long list of potential therapeutic targets and choose those most likely to lead to success, with the cost being shared evenly by NIH and industry.

But we are not stopping there. Influenza is another area where we are poised for rapid progress. In fact, NIH-funded scientists are well on their way to developing a universal vaccine. The outside of the flu virus, shown here, is coated with tiny mushroom-shaped proteins, and each of these proteins has a head and a stem.

[The graphic follows:]



Dr. COLLINS. Current vaccines target the head of that mushroom, but this mutates over time. Here you can see in yellow the changes that occurred in three different flu viruses.

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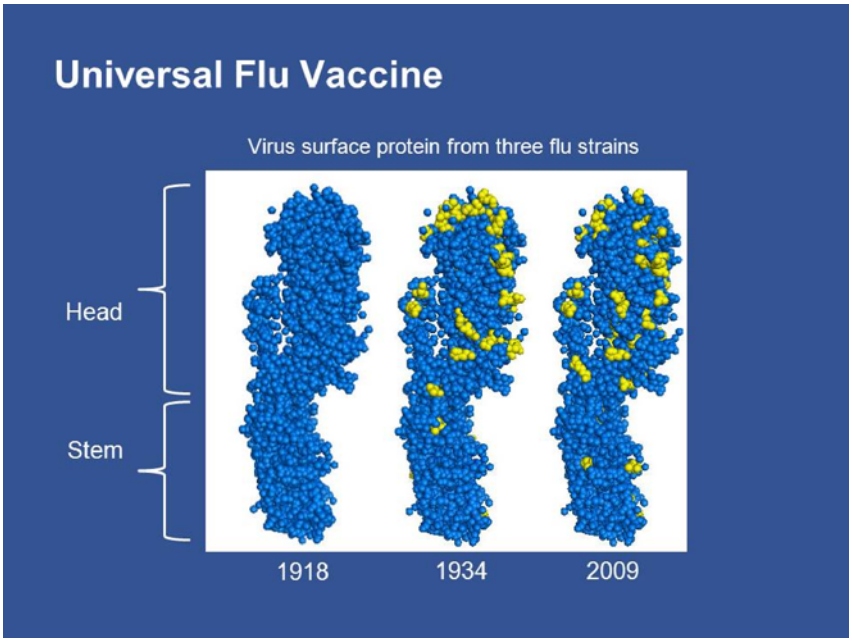


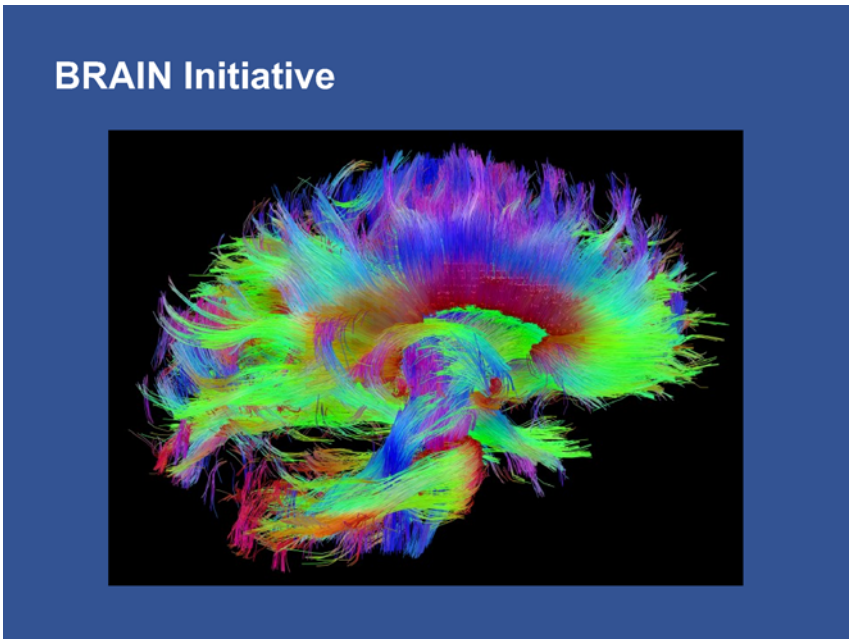
Dr. COLLINS. These changes, primarily in the head, are happening all the time. To keep up, a new vaccine must be produced every year.

On the other hand, you can see here the stem of the viral protein remains almost entirely unaltered over time. A universal flu vaccine that targets the relatively stable stem would not only eliminate the need for an annual flu shot, but would also provide protection against outbreaks like the H5N1 and H7N9 events in Southeast Asia that are causing considerable worldwide concern right now.

BRAIN INITIATIVE

Another major challenge is exploring what has been called the most complex structure in the known universe, the human brain. As you know, NIH is leading the new Brain Research through Advancing Innovative Neurotechnologies, B–R–A–I–N, BRAIN Initiative, and we are grateful for your support.

[The graphic follows:]



Dr. COLLINS. This initiative will provide a foundational platform for major advances in Alzheimer's disease, autism, schizophrenia, traumatic brain injury, epilepsy, and many other brain disorders.

But a final area of scientific opportunity that I want to highlight today involves one of our Nation's biggest and most feared killers, cancer. Until recently, our weapons for attacking cancer have been surgery, radiation, and chemotherapy, all of which can be effective, but carry risks. Recent advances have given us insights into the intricate workings of the cancer cell, and a whole new generation of

targeted therapeutics is emerging, ushering in an era of individualized precision medicine.

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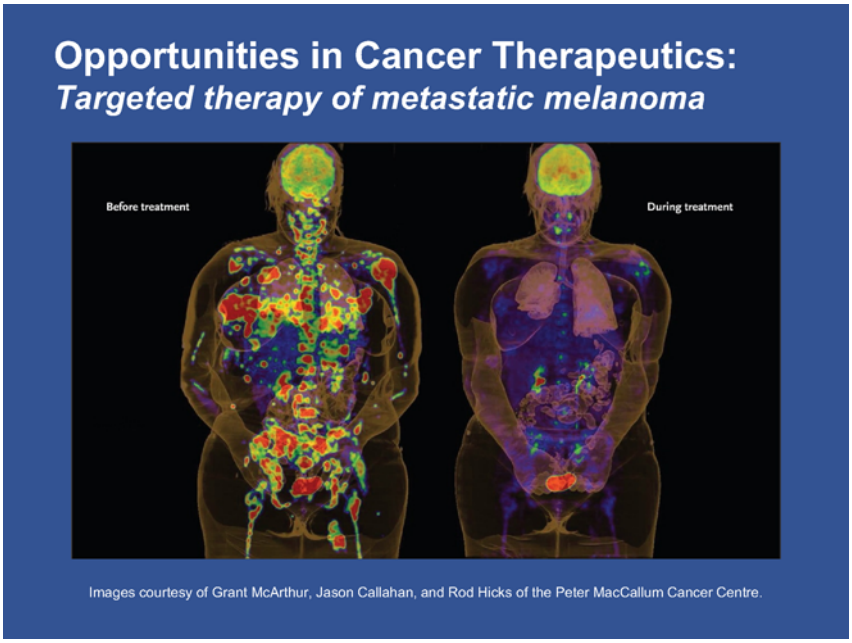

OPPORTUNITIES IN CANCER RESEARCH

Dr. COLLINS. This image on the left shows a dramatic example of just how effective such targeted therapies can be because on the left is a scan of a melanoma patient who carries a mutation and a gene that codes a protein called B-Raf. Now, B-Raf is implicated when mutated in the development of cancer. The hot spots that you see all over this individual's body indicate dividing cancer cells that have spread throughout. After treatment with a new drug targeted to block the effects of mutant RAF, those hot spots almost vanish. The promise of targeted therapy is apparent.

But now, there is a new powerful weapon in the arsenal, cancer immunotherapy, a revolutionary new approach that Science magazine named its 2013 breakthrough of the year.

[The graphic follows:]

Dr. COLLINS. This involves harnessing the body's own immune system to fight this dreaded disease. In one of those new approaches, certain types of immune cells called T-cells—you can see them here—are collected from cancer patients and engineered to produce special proteins on their surface. When these engineered T-cells are infused back into patients, they have the power to seek and destroy cancer cells.

And in this video, you can see one of those modified T-cells doing just that, actually obliterating the cancer cell.

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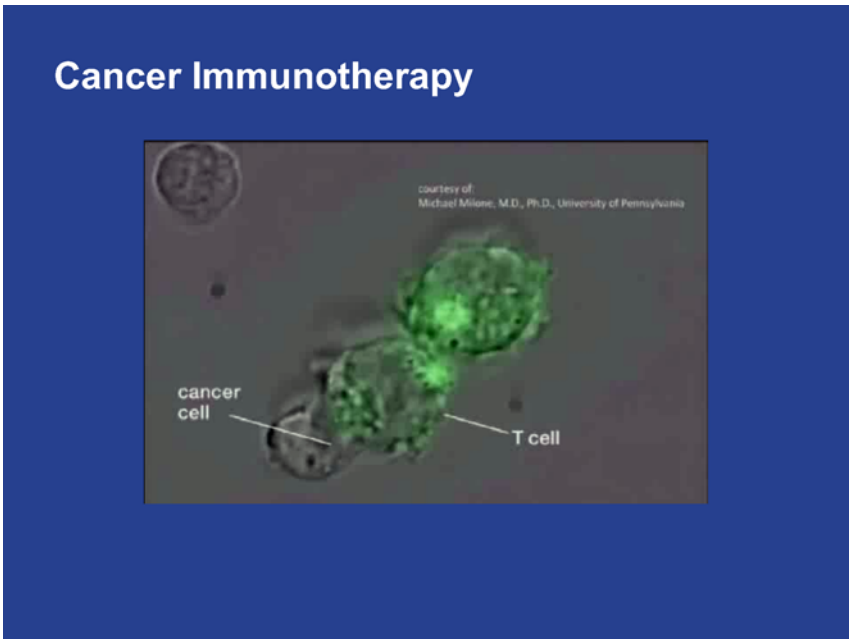

Dr. COLLINS. Knowing how to turn T-cells into little Ninja warriors required big investments in basic biomedical research over more than a decade, but the consequences are starting to be amazing.

I would like to share this story, in closing, of Emily Whitehead.

[The graphic follows:]

Dr. COLLINS. Nearly 2 years ago, this brave little girl became the first pediatric patient to be treated with a new kind of cancer immunotherapy. Emily was suffering from acute lymphoblastic leukemia, a disease that, as was pointed out by Senator Moran, now we cure 90 percent of the time with chemotherapy. But distressingly, Emily was in the 10 percent where that fails.

Her parents decided to enroll her in a pioneering cancer immunotherapy trial at the Children's Hospital of Philadelphia. Emily's T-cells were collected from her blood and re-engineered in the lab to recognize a protein found only on the surface of her leukemia cells. Those T-cells were then infused back into Emily's blood where they circulated throughout her body on a mission to seek and destroy leukemia. Just 28 days after treatment, she was cancer free, and she remains so to this day.

[The graphic follows:]

Dr. COLLINS. Here is Emily today, a happy, healthy third grader who is looking forward to celebrating her ninth birthday next month. As her mom, Kerry, puts it, "If you didn't know what happened to her and you saw her now, you would have no idea what she has been through." A wonderful story of success.

And, Senators, I believe there are a great many more Emilys on the horizon. Our Nation has never witnessed a time of greater promise for advances in medicine. With your support, we can realize our vision of accelerating discovery across the vast landscape of biomedical research. From basic scientific inquiry to human clinical trials, the National Institutes of Hope is ready to move forward.

[The graphic follows:]

Dr. COLLINS. Thank you, Mr. Chairman, for your support of NIH. My colleagues and I welcome your questions.

[The statements follows:]

PREPARED STATEMENT OF FRANCIS S. COLLINS, M.D., PH.D.

Good morning, Mr. Chairman and distinguished members of the subcommittee. I am Francis S. Collins, M.D., Ph.D., Director of the National Institutes of Health (NIH). It is an honor to appear before you today to present the Administration's fiscal year 2015 budget request for the NIH and provide an overview of our critical role in enhancing our Nation's health through scientific discovery.

As the Nation's biomedical research agency, NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to enhance human health, lengthen life, and reduce illness and disability. I can report to you that NIH leadership, employees, and grantees continue to believe passionately in this mission.

Before I discuss the tremendous strides we have made and the exciting scientific opportunities on the horizon, I want to thank you, Mr. Chairman, and Ranking Member Moran, as well as your colleagues, for the recent fiscal year 2014 Omnibus Appropriation bill. The subcommittee came together in a bipartisan way to increase funding for NIH and we are truly grateful for your action. The past year has been challenging for us: The sequester reduced funding for groundbreaking medical research and affected the morale of the scientific community. This impact was further exacerbated by the shutdown.

There is much good news to report about the science that we support. NIH has been advancing our understanding of health and disease for more than a century; scientific and technological breakthroughs generated by NIH-supported research are behind much of the gains our country has enjoyed in health and longevity. For example, deaths from heart disease have been reduced by more than 70 percent from 1950 to 2008. Cancer death rates have been dropping about 1 percent annually for the past 15 years—life expectancy gains that save the Nation billions of dollars. HIV/AIDS treatment and prevention now enable us to envision the first AIDS-free generation since this virus emerged more than 30 years ago. NIH research also has given us vaccines to protect against an array of life-threatening diseases, including cervical cancer, influenza, and meningitis. We can look forward to a future in which

advanced prevention and treatment strategies such as these allow everyone to have a significantly better chance of living a long and healthy life.

These statistics tell you how far we have come—but our aim is to go even further, faster. To this end, the Administration's fiscal year 2015 budget request for the NIH is $30.362 billion, $211 million, or 0.7 percent, above the fiscal year 2014 level. This budget request reflects the President's and the Secretary's commitment to improving the health of the Nation and to maintaining our Nation's leadership in the life sciences. The request highlights investments in innovative research that will advance fundamental knowledge and speed the development of new therapies, diagnostics, and preventive measures to improve public health.

The fiscal year 2015 budget request will enhance NIH's ability to support cutting-edge research and training of the scientific workforce. Within the Administration's fiscal year 2015 budget, we will continue to increase Research Project Grants (RPGs), NIH's funding mechanism for investigator-initiated research. NIH expects to support 9,326 new and competing RPGs in fiscal year 2015, an increase of 329 over fiscal year 2014 levels. For fiscal year 2015, NIH anticipates funding a total of 34,197 RPGs. The budget request allocates resources to areas of the most extraordinary promise for biomedical research, while maintaining the flexibility to pursue unplanned scientific opportunities and address unforeseen health needs.

While we are very grateful for any budget increase, the fully paid $56 billion Opportunity, Growth, and Security Initiative (OGSI), a program included in the President's budget, would provide an additional $970 million investment in NIH programs that would allow NIH to fund or expand a host of other cutting-edge initiatives, speeding the development of vaccines and cures, and restoring sequestration cuts to the number of research project grants.

Let me describe a few of the many areas in which NIH-supported research is opening up extraordinary opportunities to improve the health of the American public.

A major program that began this year is the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, for which thanks are due to this subcommittee for its fiscal year 2014 support. NIH is a major player in this pioneering multiagency venture that will enable the creation of new tools capable of examining the activity of billions of nerve cells, networks, and pathways in real time. By measuring activity at the scale of circuits and networks in living organisms, we can begin to decode sensory experience and, potentially, even memory, emotion, and thought. Successful pursuit of the BRAIN Initiative will revolutionize neuroscience, providing a foundational platform for major advances in Alzheimer's disease, autism, schizophrenia, epilepsy, traumatic brain injury, and many other brain disorders.

As technology allows us to tackle mind-boggling tasks like recording the activity of billions of nerve cells in the brain or determining the DNA sequence of tens of thousands of human genomes, researchers are generating enormous quantities of data at an unprecedented pace. The challenge posed by this revolution is how to store, retrieve, integrate, and analyze this mountain of complex data—and transform it into knowledge that can improve human health. To address this challenge that affects virtually all areas of biomedical research, we have just launched the Big Data to Knowledge (BD2K) initiative. The goals of BD2K are to develop and disseminate new analytical methods and software, enhance training of data scientists, and facilitate broad use and sharing of complex biomedical datasets. With sustained investment and effort, we will overcome the challenges associated with Big Data to accelerate real-world applications of basic science discoveries.

We are also excited about another area of intense interest: the development of therapeutics. Recent advances in genomics, proteomics, imaging, and other technologies have led to the recent discovery of more than a thousand risk factors for disease—biological insights that ought to hold promise as targets for drugs. But drug development is a terribly difficult and failure-prone business. To the dismay of researchers, drug companies, and patients, the vast majority of drugs entering the development pipeline fall by the wayside. The most distressing failures occur when a drug is found to be ineffective in the later stages of development—in Phase II or Phase III clinical studies—after years of work and millions of dollars have already been spent. A major reason for such failures is that scientists often have not had enough information to choose the right biological targets. If a drug is aimed at the wrong target, it won't work against the disease it was intended to treat.

With that challenge in mind, we were thrilled last month to launch the Accelerating Medicines Partnership (AMP). This unprecedented public-private effort will use cutting-edge scientific approaches to sift through a very long list of potential therapeutic targets, and choose those most likely to lead to success. Besides NIH, the AMP partners include the FDA, 10 biopharmaceutical firms and a number of

nonprofits, including patient advocacy groups. This precompetitive partnership, which will share all data openly, will initially focus on three disease areas that are ripe for discovery: Alzheimer's disease, type 2 diabetes, and the autoimmune disorders, lupus and rheumatoid arthritis. Through this team effort, we believe we can reach our shared goals of treating and curing disease faster.

Preventing disease is another top priority, and influenza is one area of prevention in which we are poised for rapid progress. Currently, to provide protection against the rapidly evolving influenza virus, a new vaccine must be produced each year and we all need to get an annual flu shot. Also, despite best efforts, the vaccine isn't always ideal. In an average year, the flu claims up to 49,000 American lives and costs the U.S. economy about $87 billion. But it does not have to be that way. NIH-funded researchers are now working on a universal flu vaccine—designed to protect people against virtually all strains of the flu for extended periods of time and, thus, potentially reduce the need for annual flu shots. Of critical importance, such a vaccine could also protect against a future global flu pandemic.

While we are several years away from having a universal flu vaccine available to the public, our researchers have already demonstrated proof of concept and are testing a number of approaches, including two-stage "prime boost" vaccines and ferritin nanoparticles. Clearly, the prospect of a universal flu vaccine is not science fiction. Early clinical studies are already underway. With sustained investment, the United States may be a few years away from realizing its potential to benefit our health and our economy.

As impressive as a universal flu vaccine would be, it is not the only trick we are teaching our immune systems. We are also aiming to harness the body's own immune system to fight cancer. Until recently, our weapons for attacking cancer have been largely limited to surgery, radiation, and chemotherapy—treatments that carry risks and cause adverse side effects. Now, after years of intense basic and translational research, we have an exciting new possibility: Cancer immunotherapy.

Researchers have long been puzzled by the uncanny ability of cancer cells to evade the immune response. What stops the body from waging its own "war on cancer?" As it turns out, our bodies have built-in checkpoints to prevent our immune systems from going into overdrive and killing healthy cells. Now, NIH-funded researchers have discovered a way to genetically modify certain white blood cells called T-cells—the soldiers of the immune system—to attack tumor cells. In this new approach, T-cells are collected from cancer patients and engineered in the lab to produce special proteins on their surface, called chimeric antigen receptors (CARs). When the modified cells are infused back into patients, they multiply and, with guidance from their newly engineered receptors, seek and destroy tumor cells. Promising results in patients with leukemia prompted Science magazine to name this its 2013 Breakthrough of the Year.

Today, I have provided a very brief overview of NIH's past successes and continuing commitment to basic, translational, and clinical research. Our Nation has never witnessed a time of greater promise for advances in medicine. With your support, we can anticipate a future of accelerating discovery across NIH's broad research landscape, from fundamental scientific inquiry to human clinical trials. The "National Institutes of Hope" is ready to move forward.

This concludes my testimony, Mr. Chairman. I look forward to your questions.

PREPARED STATEMENT OF ANTHONY S. FAUCI, M.D.

Mr. Chairman and Members of the Committee: I am pleased to discuss current and future plans for biomedical research at the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). The President's fiscal year 2015 NIAID budget request of $4,423,357,000 billion is approximately $31 million more than the fiscal year 2014 funding level ($4,392,670,000).

NIAID conducts, supports, and translates basic and clinical research into the development of diagnostics, therapeutics, and vaccines to detect, treat, and prevent infectious and immune-mediated diseases. NIAID has a dual mandate that balances research addressing current biomedical challenges with the capacity to rapidly respond to new threats from emerging and re-emerging infectious diseases and bioterrorism.

INFECTIOUS DISEASES RESEARCH

HIV/AIDS.—NIAID is leading transformational progress in basic and clinical research on HIV/AIDS. The decades-long NIAID investment in HIV/AIDS research has made the goal of an AIDS-free generation a possibility with sustained effort. NIAID continues to improve and refine HIV prevention and treatment tools, includ-

ing antiretroviral therapies to effectively manage disease and reduce HIV transmission, and pre-exposure prophylaxis to protect against HIV. NIAID also is advancing research toward the development of an effective HIV vaccine to complement existing prevention strategies. HIV vaccine development will be informed by NIAID efforts to identify immunological markers in the subset of people protected against HIV infection in the RV144 trial, the first HIV vaccine trial to show modest efficacy. The NIAID Vaccine Research Center together with several NIAID grantees are making rapid progress on ways to generate broadly neutralizing antibodies to protect against multiple strains of HIV, research that may translate to vaccines and therapeutics of global public health significance.

Years of NIAID-supported research on HIV pathogenesis and the role of HIV reservoirs have suggested the feasibility of curing some HIV-infected individuals. NIAID will investigate promising reports of a handful of infants who were born HIV-positive but now test negative for the virus following aggressive antiretroviral treatment initiated shortly after birth by supporting a clinical trial to determine if this strategy is safe and effective for other infants. NIAID also will play a major role in implementing the President's $100 million HIV/AIDS cure research initiative. As part of this effort, NIAID will support additional research on HIV latency and persistence. Understanding these processes may reveal new strategies toward a cure.

NIAID recently restructured its HIV/AIDS Clinical Trials Networks to capitalize on the growing body of promising HIV research findings and to better address current research questions. The Networks will focus on improved ways to prevent and treat HIV, tuberculosis and hepatitis C co-infections, and on research toward development of a vaccine, microbicides, and a cure.

Tuberculosis.—Tuberculosis (TB) remains a significant cause of illness and death throughout the world, especially among those also infected with HIV. NIAID recently launched a genome sequencing project that will examine the genetic diversity of TB bacteria and patterns of drug resistance to understand TB pathogenesis and to identify new drug targets and molecular mechanisms of resistance. This research will be particularly important to address the emergence of multi- and extensively drug-resistant TB. NIAID-supported scientists also are working to modify the existing antibiotic spectinomycin to bypass mechanisms of resistance to this drug. These efforts have shown promise in TB animal models.

Malaria.—NIAID continues to progress toward its goal to control, eliminate, and ultimately eradicate malaria worldwide. The development of vaccines is a critical part of this endeavor. NIAID researchers and grantees recently completed an early-stage clinical trial that showed a novel vaccine composed of weakened malaria sporozoites was safe and protected against malaria. NIAID has developed two new tests to rapidly and inexpensively detect resistance to artemisinin, a first-line antimalarial drug. NIAID also is exploring innovative methods to control the spread of malaria. For example, NIAID-funded researchers have established a bacterial infection that passes from female mosquitoes to their offspring and kills malaria parasites within the mosquitoes before they can infect humans.

Other Infectious Diseases of Domestic and Global Health Importance.—NIAID is committed to research on infectious diseases affecting global health. Influenza is among the most important infectious diseases of domestic and global concern. NIAID research addresses the challenge of seasonal influenza and prepares for the threat of an emerging pandemic. NIAID is developing and evaluating vaccines against the avian influenza strains H5N1 and H7N9 to deploy if needed to prevent further spread among humans. NIAID also is examining these vaccines paired with adjuvants—components that enhance the immune response—to provide the greatest protection with the smallest dose possible. NIAID investigators and grantees are making significant progress toward the development of a universal influenza vaccine that could generate durable protection over a period of years against a wide range of seasonal and pandemic influenza strains. Studies conducted by NIAID scientists at the NIAID Special Clinical Studies Unit in the NIH Clinical Center are providing important clues into the susceptibility and immune response of patients to influenza infection. Future studies will examine the effectiveness of new vaccines and therapeutics.

Respiratory syncytial virus (RSV) is a serious respiratory infection primarily of young children that causes significant illness and hospitalizations in the U.S. and thousands of deaths worldwide. There is no vaccine to protect infants and children against RSV. Researchers at the NIAID Vaccine Research Center recently determined the structure of a key RSV protein bound to a broadly neutralizing human RSV antibody and used it to design an experimental RSV vaccine that is effective in animal models. NIAID has advanced this groundbreaking RSV vaccine into early-

stage clinical trials in humans. Science magazine highlighted this discovery among the top 10 scientific breakthroughs in 2013.

Hepatitis C virus (HCV) is a significant cause of chronic liver disease and cancer, and often co-infects people with HIV. Traditional HCV therapies frequently have severe side effects and may not be successful in many patients. NIAID and NIH Clinical Center investigators recently led a Phase II trial of a new HCV drug, sofosbuvir. The trial demonstrated that sofosbuvir, combined with the antiviral drug ribavirin, was highly effective and well tolerated even in patients predicted to have poor outcomes with traditional HCV treatments. Sofosbuvir and similar therapies for the treatment of HCV have recently been approved, potentially revolutionizing treatment outcomes.

Antimicrobial resistance is a significant public health challenge and an NIAID priority. NIAID recently reassessed research needs for this important issue and established a Leadership Group to design, implement, and manage the clinical research agenda for a new antibacterial resistance research network. NIAID provides resources to lower the investment risk for industry, academia, and non-profit organizations to facilitate a robust pipeline of diagnostics, vaccines, and therapeutics for resistant microbes.

RESEARCH ON IMMUNOLOGY AND IMMUNE-MEDIATED DISORDERS

NIAID's commitment to research on basic and clinical immunology continues to foster important insights that ultimately will help to better treat and prevent immune-mediated disorders, including food allergy. NIAID-funded investigators recently demonstrated that female sex hormones affect the gut microbiome and promote development of autoimmunity in an animal model, providing clues into why women are more likely to be affected by autoimmune diseases. NIAID-supported researchers have made progress in understanding how exposure to certain microbes in early life, especially those found in homes with dogs, may protect against the development of asthma and other allergies. NIAID grantees also developed two urine tests to diagnose and predict rejection of a transplanted kidney. These simple tests could one day replace the invasive procedure currently used to detect organ rejection and particularly would benefit African Americans, who are disproportionately affected by organ transplant rejection.

CONCLUSION

For more than 60 years, basic and clinical research conducted and supported by NIAID on infectious and immune-mediated diseases has spurred the development of vaccines, therapeutics, and diagnostics to improve the health of millions around the world. NIAID will continue to perform the basic, clinical, and translational research critical to advancing the health of our Nation and the world.

PREPARED STATEMENT OF HAROLD E. VARMUS, M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Cancer Institute (NCI) of the National Institutes of Health (NIH). The fiscal year 2015 NCI budget of $4,930,715,000 includes an increase of $7,944,000, or 0.2 percent, compared to the fiscal year 2014 level of $4,922,771,000.

OVERVIEW OF NCI RESEARCH PRIORITIES

This is an era of remarkable opportunity in cancer research. Armed with broad knowledge about how various cancers arise and with powerful new research tools, the NCI is well equipped to accelerate progress towards preventing, diagnosing, and treating cancer more effectively. This era of opportunity is due in significant part to the subcommittee's consistent support for biomedical research at NCI and NIH.

The resources that you provide allow NCI to address an ambitious challenge: reducing the incidence, morbidity, and mortality for all of the many types of cancer, with tangible benefits for all Americans. The fiscal year 2015 budget will allow the NCI to build on the tremendous progress in many areas of cancer research, with the aim of improving outcomes for patients with all types of cancer.

I will summarize some recent accomplishments and highlight new opportunities in five areas of NCI-supported research—genomics, cancer immunology, targeted therapeutics, bioinformatics, and prevention—to illustrate the breadth and pace of NCI's progress.

The Cancer Genomics research that NCI supports has dramatically altered our understanding of how cancer develops, identified the molecular signatures that can

be used to diagnose and categorize cancer more precisely, and provided new targets for therapeutic intervention. For example, two major initiatives—TCGA (The Cancer Genome Atlas) and TARGET (Therapeutically Applicable Research to Generate Effective Treatments)—have addressed nearly twenty common adult cancers and several less common cancers that occur in adults and children, revealing both tissue-specific patterns of genetic changes and changes that are common to several types of cancers. TCGA is a joint initiative of the NCI and the Human Genome Research Institute. During the past year, TCGA published comprehensive characterizations of acute myeloid leukemia, endometrial cancer, and clear cell renal carcinoma, among others. While every cancer is distinct genetically, many changes in the genome are shared among a wide array of cancer types, and each type of cancer has distinct patterns that often reflect exposure to carcinogenic agents, such as tobacco smoke and ultraviolet radiation. As these massive surveys come to conclusion, the NCI's Center for Cancer Genomics is leading efforts to make full use of the TCGA results, including the best ways to incorporate genomic findings into the design of clinical trials.

Some of the surprising findings from the TCGA and TARGET projects—such as the involvement of genes that govern the chemistry of chromosomal proteins, that influence cell metabolism, and that guide the processing of RNAs and proteins—are influencing the study of cancer biology throughout the NCI's programs. TCGA and TARGET will certainly enlarge our understanding of carcinogenesis and will likely open new frontiers for preventing, diagnosing, and treating cancers.

Cancer immunology is a rapidly advancing field that, in just the past few years, has dramatically altered our understanding of host defenses in response to cancers. It has also produced new and well-validated methods for treating cancer using antibodies that attach to proteins on cancer cell surfaces and using methods that modulate the complex behavior of the immune system to attack cancer cells.

For several years, monoclonal antibodies against cancer cell proteins have been used to treat blood cancers, such as certain lymphomas and leukemias, and subsets of several types of solid tumors, such as breast and colorectal cancer. More recently, immunotoxins have been created by genetic engineering to fuse antibodies with parts of bacterial toxins to selectively kill cancer cells. For example, such immunotoxins developed in the NCI intramural program have induced remissions in late stage cases of mesothelioma, ovarian cancer, triple-negative breast cancer, drug-resistant hairy cell leukemia, and childhood acute lymphoblastic leukemia.

There is also great optimism within the science community about modulating the immune system by introducing novel antigen receptors into cancer-killing T cells and especially by infusing antibodies that interfere with a system that impedes the immune response to cancer cells. These "immune-modulating" antibodies have recently received FDA approval, and other antibodies that bond other immune cell regulators may soon follow. In 2011, FDA approved a monoclonal antibody, called ipilimumab, to treat advanced melanoma. Some patients with metastatic melanoma being treated with ipilimumab are still alive several years after completing treatment. In 2013, another promising antibody to treat melanoma—lambrolizumab—received "breakthrough" designation by the FDA, helping expedite its development and further use in clinical trials, with the possibility of an expedited FDA review. In recognition of these and other recent achievements in the field of immunology, and the promise of further developments, "cancer immunotherapy" was named this year's Breakthrough of the Year by Science magazine.

Targeted therapies, based on the use of drugs that inhibit specific proteins implicated in the behavior of cancer cells, are now being developed and tested for their effects in patients with many types of cancer. Over the past decade, FDA has approved several drugs that rely on this therapeutic approach to treat cancers of blood cells, lung cancer, melanoma, and other cancers, and many more are in development. This activity has accelerated because of discoveries in genomics, cell signaling pathways, chemistry, and structural biology, and with the identification of new ways to inhibit proteins that are required for the integrity of cancer cells.

Mutant RAS proteins are perhaps the most prominent potential targets for new therapies that the academic and commercial research sectors have thus far failed to target with inhibitory drugs. The importance of the RAS gene family in cancer has been clear for over 30 years; one family member, K–RAS, is mutated in more than 90 percent of pancreatic adenocarcinomas, about 40 percent of colorectal cancers, and about 25 percent of lung adenocarcinomas. For this reason, the NCI recently launched the RAS Project, a large-scale collaboration between investigators at the NCI's Frederick National Laboratory for Cancer Research and those in NCI's intramural and extramural communities. The RAS Project is motivated in part by new developments in the study of RAS proteins, including new information about their structural properties, binding of mutant RAS proteins to mutant-specific in-

hibitors, interactions with other cellular proteins required for function, and new tests for genes required to allow RAS mutants to exert their effects.

Still, while pursuing a path that leads to "precision medicine," the NCI must also maintain its capacity to test new ways to deploy the currently dominant means of therapy. For instance, a recent study of patients with metastatic prostate cancer showed markedly increased survival in men who received chemotherapy when starting anti-androgenic hormone therapy, a result that is likely to change clinical practice for a cancer that continues to kill about 30,000 American men annually.

Drug resistance commonly emerges in cancers being treated with either traditional chemotherapies or novel targeted therapies, allowing disease to progress. Over the past decade, NCI-supported studies have revealed several mechanisms by which resistance occurs, including additional mutations affecting the target molecules, mutations in related genes, and changes in gene expression. In some cases, especially chronic myeloid leukemias, drugs that overcome resistance have been identified, developed and FDA-approved. But in other situations, resistance to targeted drugs remains a major impediment to success, and the NCI is making major investments to study this problem.

Bioinformatics, the management of enormous sets of molecular and clinical data is a critical component of NCI's toolkit to study cancer in all of its manifestations. In work that ranges from cancer genomics, to cell signaling, and to clinical trials, the proper collection, analysis, storage, retrieval, and distribution of "big data" are critical elements of the Institute's charge. The NCI's Center for Bioinformatics and Information Technology (CBIIT) is addressing these responsibilities, in conjunction with NCI divisions. Part of the current effort requires the costly development of "cloud computing" to work with the vast (petabyte) amounts of genomic data generated by TCGA, TARGET, and other projects, and to assemble and ultimately integrate clinical data with genomic data in manageable forms to promote further discovery and improve cancer care.

Prevention of cancer remains NCI's most desired goal. While complete avoidance of cancer may be impossible, since cancers often arise through spontaneous mutations, the control of tobacco use, vaccination against cancer-causing viruses (human hepatitis B virus and human papillomaviruses), sunlight avoidance, and regulation of dietary and carcinogenic substances (such as asbestos) have already reduced the incidence and the mortality rates of many cancers. For instance, between 2001 and 2010, largely due to the earlier reductions in tobacco use, there was a 25 percent decrease in male death rates and an 8 percent decrease in female death rates due to lung cancer, the major cause of death from cancer in the United States. Likewise, vaccination with current HPV vaccines can drastically reduce the incidence and mortality of several types of cancer, including cervical, anal, and oropharyngeal cancers that are caused by infection with certain strains of HPV.

Still, NCI recognizes that these successes are incomplete, and therefore invests heavily in efforts to address several pertinent behavioral and biological questions. For instance, despite dramatic declines in the use of tobacco, about 18 percent of Americans continue to smoke. New approaches are needed to convince young people not to use tobacco and to convince current smokers to quit. Use of HPV vaccines remains far from the desired levels among adolescent girls and boys in the United States, as the February 2014 report from the President's Cancer Panel emphasized. Better methods to promote the use of these potentially lifesaving vaccines are needed, at the same time as the dosing schedules and the protective breadth of the vaccines are improved.

CONCLUSION

An important measure of the overall success of NCI's work is the annual "Report to the Nation," which describes trends in the incidence and death rates in the United States for many types of cancer. As has now been true for over a decade, the most reliable indicator—death rates from all cancers combined for men, women, and children—continues to decline by about one and a half percent per year. This reduction represents the savings of an enormous number of years of life and can be ascribed in large measure to the work of the NCI to prevent and treat cancers more effectively.

Still, although mortality rates have been decreasing for most cancers, progress has not occurred as rapidly as desired, and for some cancers the numbers have not improved—or have worsened. Thus, much work remains. But the overall success apparent from both the public health data and recent achievements in the laboratory and clinical sciences inspires the NCI's conviction that expanded efforts on all frontiers of cancer research will produce better health in the United States and around the globe.

PREPARED STATEMENT OF GARY H. GIBBONS, M.D.

Mr. Chairman and distinguished members of the subcommittee: I am pleased to present the President's budget request for the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). The fiscal year 2015 budget of $2,987,685,000 includes an increase of $4,948,000 over the fiscal year 2014 enacted level of $2,982,737,000.

NHLBI's highest priorities for research investment are conditions that contribute substantially to the global burden of disease. Heart and lung diseases are the leading causes of death, disability, and rising healthcare costs from non-communicable diseases in the United States and worldwide. Research supported by the NHLBI has contributed to dramatic improvements in longevity, quality of life, and the wealth of the Nation. Deaths from cardiovascular disease, for example, have dropped by 70 percent in the past 40 years. This success reflects a balanced approach to supporting discovery science that spans basic, clinical, and population research. As accountable stewards seeking to maximize the public's return-on-investment, we are committed to continually improving our approach to strategic priority-setting and systematic evaluation of our portfolio to ensure the highest possible impact on science and health.

Reflecting upon the NHLBI's legacy of success, many of the previous advances involved interventions at the latter stages of chronic disease. The fiscal year 2015 budget envisions a research agenda that elucidates the underlying mechanisms of disease such that clinicians can more accurately predict at-risk individuals and tailor preventive interventions for disease long before symptoms and irreversible damage occur. Our strategic vision is guided by the breathtaking scientific opportunities at hand and public health needs, in consultation with domain-experts at the leading edge of discovery science. The fiscal year 2015 budget continues a journey toward predictive, preventive precision medicine that holds promise for turning research-to-results, continuing the dramatic decline in the burden of chronic disease in our Nation.

UNPRECEDENTED SCIENTIFIC OPPORTUNITIES

Sustained investments in fundamental discovery science have led to new tools and technologies that stand to revolutionize medical research and clinical practice. Biomedical advances in congenital heart disease (CHD), the most common structural birth defect, have led to dramatic improvements in infant survival over the past 50 years, now with more adults living with CHD than children. However, current palliative approaches that repair birth defects have limitations that compromise the length and quality of life. Recent NHLBI-supported research, applying the latest genomic technologies, has identified spontaneous genetic mutations that increase the risk of CHD. This breakthrough finding is beginning to unlock the mysteries of CHD, helping to define what goes awry during the formation of the heart and lay the foundation for preventing or fixing defects in the womb. To that end, NHLBI is investing in regenerative medicine research to enhance the capacity of the heart to repair itself. The 2012 Nobel Laureate, Shinya Yamanaka, is part of a large interinstitutional team of NHLBI-funded investigators studying how to use a child's own cells to repair a congenital defect or create a tissue graft that could grow as a child ages.

NHLBI investments in reparative biology and tissue bioengineering may also hold promise for accelerating new drug development platforms in partnership with the private sector. For example, NHLBI-funded investigators at Stanford University are using stem cells derived from adult tissue in a laboratory to create heart cells and model diseases such as those that perturb the electrical system of the heart in atrial fibrillation. These models are being used to more efficiently screen many novel drugs to determine efficacy as well as potential toxicities, augmenting the discovery pipeline.

PREEMPTING AND PREVENTING CHRONIC DISEASE

New scientific discoveries hold promise for making public health inroads to halt chronic diseases before they become debilitating. In sickle cell disease (SCD), for example, we have made great strides in reducing complications from the disease, such as penicillin to prevent fatal infections in infants, transfusions to reduce stroke risk, and hydroxyurea to reduce pain and hospital admissions. While these advances have extended lifespans from childhood into the sixth decade of life, they target complications not the disease itself—a disease that disproportionately affects African Americans (about 1 in 500 births). We recently funded a new program that we hope will lead to the next generation of SCD treatments. Particularly exciting are studies that

are attempting to raise fetal hemoglobin levels (the most powerful known modifier of SCD severity) through modulation of a gene called Bcl11A that is involved in the switch from fetal to adult hemoglobin during development. These studies open the door to potential treatments that can reactivate the fetal hemoglobin gene to inhibit the sickle cell shape change of red blood cells, which could preempt disease progression.

Chronic obstructive pulmonary disease (COPD), the third leading cause of death, is a prime example of a chronic disease in which biomedical research advances have ameliorated symptoms; yet most interventions fail to dramatically alter the natural course of the disease. There is a critical need to identify at-risk individuals earlier in the disease process to prevent disease progression. NHLBI's COPDgene study is integrating genetics and imaging studies to characterize pre-clinical subtypes of COPD. Such characterization can enable clinicians to detect subtle changes in lung function and structure long before symptoms develop, conventional clinical tests show abnormalities, or progressive lung damage occurs. This leading-edge research points to a horizon of individualized, precision medicine to preempt chronic lung disease.

TRANSLATING DISCOVERIES INTO PUBLIC HEALTH IMPACT

While basic science is the cornerstone of scientific discovery, it is the beginning of a long path to public health impact. NHLBI has been a leader in traversing this road. Noted research initiatives like the Framingham Heart Study first identified the cardiovascular disease risk factors now addressed in routine physicals, which led to basic research that won Brown and Goldstein the Nobel Prize for their research on cholesterol metabolism—setting the stage for the development of statin drugs.

We are currently amidst the unfolding of a similar story. The recent discovery of a mutation in the gene PCSK9 among a family with very low LDL cholesterol levels and reduced risk of heart attack has led to basic science discoveries and the rapid development of PCSK9 inhibitors. This public-private partnership is moving toward potential widespread clinical use as the next generation of cholesterol lowering drugs.

We now know, however, that we must look beyond one-size-fits-all treatments. Population science and genetics research have clearly demonstrated individual differences not only in predisposition to disease but also in treatment response. For example, 26 million Americans currently suffer from asthma—the leading cause of missed school days for children and a driver of preventable hospitalizations and emergency room visits. Asthma disproportionately affects African Americans; African American children are twice as likely to have asthma as white children and, as adults, are two to three times more likely to die of asthma than any other racial or ethnic group. While effective treatments exist, they do not reach all of those in need. NHLBI will be seeking applications focused on identifying barriers and testing strategies to enhance the implementation of evidence-based practices in diverse communities across the Nation. Beyond the current treatments, next generation therapies should target these differences to achieve maximal benefit. NHLBI's multi-center clinical trial network, AsthmaNet, is beginning the Best African American Response to Asthma Drugs (BARD) study to compare the effectiveness of different treatments on the management of asthma in African Americans. BARD will also assess how genetics may influence an individual's response to the treatments, which could be a paradigm shift in addressing challenges like disparities in asthma care.

CONCLUSION

We are in the midst of a very exciting period in science in which the capacity to enhance human health has never been greater. New tools and technologies are daring us to envision a future that is unburdened by chronic heart, lung, and blood diseases—not only ensuring wellness but also increasing economic productivity and reducing healthcare costs. For example, research shows that treating patients at moderate risk for cardiovascular disease with statin drugs to lower cholesterol can reduce annual medical spending by up to $430 million. Imagine how much can be saved by preventive interventions earlier in the disease course before symptoms begin and the costs of treatment rise dramatically. By achieving that goal, the return-on-investment of biomedical research will strengthen both the health and the wealth of the Nation.

PREPARED STATEMENT OF STORY C. LANDIS, PH.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH). The fiscal year 2015 NINDS budget of $1,608,461,000 includes an increase of $22,664,000 over the comparable fiscal year 2014 level of $1,585,797,000. NINDS supports research to reduce the burden of neurological disorders, from basic studies of the normal brain through clinical trials of prevention and treatment interventions. Today, I will make four points: (1) the burden of neurological disorders is enormous; (2) past NINDS research has paid off; (3) opportunities for future progress are extraordinary; and (4) we have well informed plans to exploit these opportunities.

BURDEN OF NEUROLOGICAL DISORDERS

Nearly 800,000 Americans experience a stroke each year, and 15 to 30 percent of the 6.8 million stroke survivors alive today suffer permanent disability.[1] Traumatic brain injury (TBI) is the leading cause of death and disability in children and young adults, common among the elderly, and a major concern for the military and veterans. In the United States, 2.5 million people receive emergency care for a TBI each year, and millions more suffer mild TBI (concussions). Epilepsy affects 2.3 million Americans, including 1 in 26 people at some time in their lives. Alzheimer's disease is receiving increasing attention, but most people are less aware that frontotemporal dementia (FTD) is the most common dementia in people under age 60, and vascular dementia, which affects blood vessels in the brain, is the second most common dementia overall and is so closely intertwined with Alzheimer's disease that most dementia patients have a combination of the two. Parkinson's disease, spinal cord injury, cerebral palsy, multiple sclerosis, and hundreds of rare diseases that affect children and adults add to the immeasurable human and economic burden.

PROGRESS FOR PATIENTS AND FAMILIES

NINDS research drives progress directly, and indirectly catalyzes private sector advances. NINDS studies on risk factors and prevention contributed to a decline in the age-adjusted stroke death rate by 35.8 percent from 2000 to 2010; the actual number of stroke deaths fell 22.8 percent.[2] NINDS research developed the only approved emergency drug therapy that restores blood flow to the brain following stroke, increasing likelihood of recovery with little or no disability by 30 percent. Research has also demonstrated, defying conventional wisdom, a wider window of opportunity for stroke rehabilitation—even patients who start rehabilitation as late as 6 months after a stroke can improve, and patients can continue to improve 1 year after a stroke. For people with epilepsy, an implantable device approved this year senses impending seizures and delivers electrical pulses to stop them. Long-term NINDS research provided the essential foundation for private sector development of this device. Similarly, NINDS research directly and indirectly contributed to deep brain stimulation (DBS) therapies now in use for Parkinson's, essential tremor, and dystonia and under clinical testing for many other disorders, as well as to development of drugs for multiple sclerosis—10 are now on the market, including the first oral drugs. Overall, the private sector has nearly 450 medicines in development for neurological disorders, which would not be possible without the foundation of NIH research.[3]

EXTRAORDINARY OPPORTUNITIES

Science and technology are opening unprecedented opportunities for progress against neurological disorders. Studies on the normal brain build the foundation. Notable recent advances, for example, revealed how the brain clears out debris during sleep, how molecular structures called ion channels control electrical activity, and the first human "connectome" maps, providing astonishing views of the basic wiring diagram of living, thinking human brains. Advances in stem cell biology now enable researchers to reproduce in cell culture key steps in amyotrophic lateral sclerosis (ALS) and other disorders using brain cells derived from patients' own skin cells. Basic science has led to new insights that explain how chronic pain is wired

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[1] Statistics for stroke, TBI, and epilepsy from U.S. Centers from Disease Control and Prevention www.cdc.gov

[2] Circulation 2014; 129:e28–e292

[3] 2013 Report: Medicines in Development for Neurological Disorders, Pharmaceutical Researchers and Manufacturers of America http://www.phrma.org/innovation/meds-in-development

in the brain, what happens in the brain following a concussion, and how cell-to-cell propagation of abnormally folded proteins could drive progression of Parkinson's, Alzheimer's, and other neurodegenerative disorders. New gene sequencing methods and high throughput gene silencing technologies have accelerated the discovery of genes that cause epilepsy and revealed potential new drug targets for Parkinson's disease. In a few dramatic cases, gene discoveries have led directly to treatments that help patients with rare disorders, including subtypes of dystonia and childhood neurodegenerative disease, but more often painstaking translational research is required to advance genetic and other discoveries toward therapies. Among the many examples, promising reports in laboratory animals this year demonstrated a drug therapy that prevented the development of epilepsy, cell transplants that controlled seizures, natural growth factor rescue of neonatal brain injury, therapies that improved cognition in Down syndrome, and a hand neuroprosthesis that restored touch sensation as well as movement.

PROGRAMS AND PRIORITIES

NINDS relies heavily upon the wisdom and ingenuity of researchers throughout the United States to propose and evaluate the best scientific opportunities. Complementing investigator-initiated programs, NINDS initiatives target unmet opportunities or public health needs. Institute priorities reflect strategic and disease-specific planning that engages the scientific community and the public, and rigorous evaluation of programs, closing those that have met their goals or are no longer appropriate for today's science. Recent plans focused on stroke, epilepsy, Parkinson's disease, and Alzheimer's Disease-Related Dementias. Among recent initiatives:

—the Stroke Trials Network will determine more quickly and at less cost what treatment, prevention, and rehabilitation strategies work best.
—new Epilepsy Centers without Walls will target Sudden Unexplained Death in Epilepsy (SUDEP) and disease modification or prevention.
—the Parkinson's Disease Biomarkers Program is developing assessment tools that will overcome roadblocks to more effective clinical trials.
—the International TBI Research Initiative, coordinated with the European Union and the Canadian Institute of Health Research, will answer questions on care and classification of TBI that have confounded development of interventions.
—two major cooperative studies are investigating the long-term changes in the brain years after a single TBI or multiple concussions, coordinated via the Foundation for NIH's Sports and Health Research Program, which was established with a donation from the National Football League.
—the NeuroBioBank, NINDS Human Genetics Repository, Federal Interagency TBI Research database, Common Data Elements Program, and an epilepsy clinical genetics data repository are examples of new and continuing resource initiatives that empower individual investigators and promote data sharing.

Finally, and most ambitiously, the President's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative will dramatically improve tools to understand heretofore unapproachable questions about how networks, or circuits, of brain cells enable us to perceive, think, and act. There are many reasons for confidence that this basic research initiative will ultimately advance progress against disease. Autism, dystonia, and epilepsy, for example, are fundamentally disorders of brain circuitry, and stroke, Parkinson's, and Alzheimer's disease disrupt brain circuits as nerve cells die. Even with our limited understanding of brain circuits and imprecise technologies for altering them, interventions that compensate for malfunctioning brain circuits already produce remarkable results. For example, DBS reverses symptoms for many people with Parkinson's disease and dystonia, and paralyzed people have controlled a robotic arm by signals directly monitored from their brains' movement control circuits. It is perhaps obvious that better understanding of brain circuits and tools to influence their activity would greatly improve these interventions, but history teaches that the most important payoffs of the BRAIN Initiative, as for basic research generally, may be entirely unforeseen.

PREPARED STATEMENT OF CHRISTOPHER P. AUSTIN, M.D.

Mr. Chairman, Ranking Member, and Members of the Committee: Thank you for the opportunity to present to you the President's budget request for the National Center for Advancing Translational Sciences (NCATS) for fiscal year 2015. The fiscal year 2015 budget for NCATS is $657,471,000, which represents an increase of $25,075,000 over the fiscal year 2014 level of $632,396,000. The request includes $471,719,000 for the Clinical and Translational Science Awards (CTSA) program and $29,810,000 for the Cures Acceleration Network (CAN).

TRANSLATIONAL RESEARCH

In recent years, biomedical research has led to significant advances in our understanding of human biology. We have sequenced the human genome, explored the potential of stem cells, and discovered RNA interference. All of these advances have been celebrated as holding enormous promise for improving human health, but the road from promise to tangible improvements in public health has been long, complex and full of obstacles. NCATS aims to turn these game-changing discoveries into treatments for patients by addressing the "translational sciences" needed to close the gap. Translational sciences comprise the process of turning observations in the laboratory and clinic into effective interventions that improve the health of individuals and the public—from diagnostics and therapeutics to medical procedures and behavioral changes.

NCATS takes a system-wide approach to diseases and the translational science process. It serves as an "adaptor" to connect basic, clinical and public health research and as a "convener" for disparate organizations that play roles in the process of turning discoveries into health improvements. Every NCATS initiative is a collaboration with partners in the public, private, government or nonprofit sector. The Center is committed to developing technologies and paradigms that improve the efficiency and effectiveness of one or more steps in the translational process, demonstrating that these innovations work in specific use cases, and disseminating the translational advances widely to catalyze improvements in all translational efforts with the ultimate and critically important goal of improving health.

MISSION INTO ACTION

One NCATS initiative that exemplifies these goals is the Discovering New Therapeutic Uses for Existing Molecules program. This program matches academic research groups with pharmaceutical companies to explore new disease indications for investigational compounds that are no longer being pursued by the pharmaceutical companies. The aim is to address several challenges in the translation process: the need for treatments for the several thousand diseases that have no effective therapy, the complicated process of negotiating agreements between parties who want to work together, and the largely ad hoc process by which academic and pharmaceutical researchers develop collaborative projects. In fiscal year 2013, NCATS funded nine projects covering eight disease areas, including Alzheimer's disease, Duchenne muscular dystrophy and schizophrenia. The program already has resulted in positive outcomes. Within 3 months of the grantees receiving funds, three compounds were being tested in humans for new uses—two to treat schizophrenia and one to treat Alzheimer's disease. In addition, the time to establish collaborations between industry and academics has been shortened to only 13 weeks from the more typical 9 months to a year. NCATS will solicit a second group of projects in fiscal year 2014.

The NCATS emphasis on innovation is central to its collaboration with the National Eye Institute and Organovo (which makes 3–D tissue printers) to develop 3–D, architecturally accurate eye tissue. Such tissues have the potential to accelerate the drug discovery process—enabling treatments to be developed faster and at a lower cost—by giving researchers a more accurate view of how drugs will behave in human cells before those drugs ever enter clinical trials.

NCATS serves as a catalyst to increase the efficiency of the translational ecosystem, as illustrated by the formation of a research team that included scientists from the Johns Hopkins School of Medicine and the NCATS Assay Development and Screening Technology Laboratory. This team developed new methods to overcome several translational roadblocks and was able to demonstrate their effectiveness by identifying a promising new compound that prevents the death of cells in the eye from glaucoma, a disease that can lead to blindness. Working together, the collaborators were able to solve a problem that none of them could address alone.

TRANSLATIONAL RESEARCH SPECTRUM

Strengthening and supporting the entire spectrum of translational research with the ultimate aim of improved public health is a top priority for NCATS, and the CTSA program is crucial for these efforts. The CTSA program develops new technologies, methods, resources and operational paradigms that catalyze clinical research progress, and supports the training and career development of translational researchers. In June 2013, the Institute of Medicine (IOM) issued a report following a review of the CTSA program. The report recommended that NCATS take a more active role in the program's governance and direction, formalize the evaluation processes of the program, advance innovation in education and training programs, and

ensure that the patient community participates in all phases of research. Since the publication of the report, the Center has increased programmatic and fiscal management of the grants that support the CTSA program and has streamlined the governance of the consortium, consulting closely with the CTSA Principal Investigators. A Working Group of the NCATS Advisory Council was established in December 2013 to provide input on measurable objectives for the program. The Working Group will submit its report to the NCATS Advisory Council in May 2014.

FOCUS ON RARE DISEASES

NCATS is deeply committed to developing treatments for rare diseases, which are defined in the U.S. as affecting fewer than 200,000 individuals. There are approximately 6,500 rare diseases, but only 250 have treatments. The NCATS Therapeutics for Rare and Neglected Diseases (TRND) program advances potential treatments for rare and neglected diseases to first-in-human trials, an approach known as "de-risking." This strategy makes new drugs more commercially attractive to biopharmaceutical companies, despite the small patient population that is characteristic of these diseases. For example, in 2013, a clinical trial was started to evaluate a drug candidate called cyclodextrin as a possible treatment for Niemann-Pick disease type C1 (NPC1), a rare and fatal genetic brain disease affecting children. A TRND-led team of more than 20 investigators from NIH, academia, a pharmaceutical company, and patient groups developed cyclodextrin as a treatment as well as an NPC biomarker to guide its clinical development. An Investigational New Drug application for cyclodextrin was approved by the FDA, and a Phase I clinical trial currently is ongoing.

CURES ACCELERATION NETWORK

CAN was authorized to advance the development of high-need cures and reduce significant barriers between research discovery and clinical trials. At NCATS, CAN is intended to advance initiatives designed to address scientific and technical challenges that impede translational research.

Currently, CAN supports the Tissue Chip for Drug Screening Program, which is a partnership with the Defense Advanced Research Projects Agency (DARPA) and the FDA to develop 3-D human tissue chips that accurately model the structure and function of human organs, such as the lung, liver and heart. These devices will enable researchers to predict harmful health effects of new drugs more accurately, thus addressing one of the main reasons that drug studies often fail.

NCATS has had success moving projects forward with its rare disease therapeutics program, but there are significantly fewer groups working on developing medical devices, for which there is a great need. NCATS could launch a comprehensive collaborative effort to accelerate device development as part of the next phase in the CAN program.

CONCLUSION

These projects are just a few examples of the exciting and innovative activities underway at NCATS. Though the Center is still relatively new, early successes demonstrate how its distinctive approaches can help solve some of the most challenging problems in translational science. We will build on our accomplishments over the past 2 years to accelerate our programs further in fiscal year 2015. I look forward to sharing more of our achievements with you as NCATS continues to evolve.

[CLERK'S NOTE.—The following Institutes of the National Institutes of Health did not appear before the subcommittee this year. Chairman Harkin requested these Institutes to submit testimony in support of their fiscal year 2015 budget request. Those statements follow:]

PREPARED STATEMENT OF LINDA S. BIRNBAUM, PH.D., D.A.B.T., A.T.S.

Mr. Chairman and Members of the Subcommittee: I am pleased to present the President's budget request for the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH). The fiscal year 2015 NIEHS budget of $665,080,000 includes an increase of $556,000 from the comparable fiscal year 2014 level of $664,524,000. The NIEHS Strategic Plan, Advancing Science, Improving Health continues to guide efforts toward fulfilling our mission to discover how the environment affects people in order to prevent both acute and chronic illness.

BREAST CANCER

NIEHS continues its robust investment into environmental factors affecting breast cancer, with the goal of learning how we can prevent this widespread disease. NIEHS and the National Cancer Institute (NCI) collaborated to support the Interagency Breast Cancer and Environmental Research Coordinating Committee, whose report, Prioritizing Prevention, recommends strategies to mitigate the environmental causes of breast cancer. NIEHS supports several major epidemiological and translational breast cancer initiatives. The Breast Cancer and the Environment Research Program is a transdisciplinary initiative cosponsored by NCI and NIEHS, in which basic scientists, epidemiologists, clinicians, and community partners work together to examine the effects of environmental exposures that may predispose a woman to breast cancer throughout her life, including exposures during puberty, menopause, pregnancy, and other "windows of susceptibility." The NIEHS Sister Study has recruited a cohort of 50,884 U.S. and Puerto Rican women with a sister diagnosed with breast cancer, to prospectively study environmental and genetic factors that influence breast cancer risk and survival. More than 1,500 incident breast cancers have been diagnosed to date. A May 2013 publication from these researchers showed that DNA methylation profiling in blood samples may hold promise for breast cancer detection and disease risk prediction. The Agricultural Health Study, a collaborative effort by NCI, NIEHS, the National Institute for Occupational Safety and Health (NIOSH), and the Environmental Protection Agency (EPA), includes a comprehensive evaluation of many commonly used herbicides and pesticides and their potential impact on risk of breast cancer among 32,000 women who are married to pesticide applicators (primarily farmers).

ENVIRONMENT AND AUTOIMMUNITY

NIEHS supports scientists who are exploring how environmental exposures can cause immune system dysfunction. There is evidence that autoimmune diseases likely involve an environmental component. Therefore, the Environmental Autoimmunity Group in the Clinical Research Program at NIEHS is looking at the relationship between environmental factors and autoimmune disease. Autoimmune diseases result from an immune response directed against the body's own tissues and they collectively afflict approximately 24.5 million Americans, with women disproportionately affected. The cause(s) of autoimmune disorders remain largely unknown and are likely multifactorial involving both genetic and environmental influences. In 2013, NIEHS released a Funding Opportunity Announcement (FOA) to enable a better understanding of the links between exposures and autoimmune disease.

NIEHS continues to support autoimmune disease research in the underserved community of Libby, Montana where the population has been exposed to asbestos minerals as a byproduct of vermiculite ore mining. Of particular concern is early childhood exposure, since susceptibility may be increased during this life stage. Recent efforts to characterize children's exposure in Libby estimated up to 15 times higher levels of airborne asbestos concentrations during outdoor activities and 73 percent of the study participants indicated these activities occurred in the presence of children.[1] NIEHS grantees are investigating whether childhood asbestos exposures in Libby are associated with pulmonary disease later in life.

ENVIRONMENT AND NEUROLOGICAL DISORDERS

Evidence indicates there is both an environmental and genetic component in neurological disorders. NIEHS funds research to advance the understanding of environmental factors and gene-environment interactions related to neurodegenerative diseases and to help create new prevention and treatment approaches. At the NIEHS Centers for Neurodegeneration Science (CNS) and in partnerships with the National Institute of Neurological Disorders and Stroke (NINDS) and National Institute on Aging (NIA), teams of top scientists from different disciplines collaborate to examine the root causes of neurodegenerative diseases. CNS researchers study how exposure to pesticides, metals (e.g. arsenic, lead), and other chemicals affect the development of neurodegenerative diseases such as Parkinson's and Alzheimer's disease. NIEHS recently published two Funding Opportunity Announcements to expand neurological research: one on environmental exposures and Alzheimer's disease, and the other on environmental exposures and neurodegenerative disease.

[1] Ryan PH et al. Childhood exposure to Libby amphibole during outdoor activities. May 22, 2013. J. Expo. Sci. Environ. Epidemiol. Published online at: http://www.ncbi.nlm.nih.gov/pubmed/?term=PMID%3A+23695492

Autism is a highly variable neurodevelopmental disorder, which is likely influenced by environmental exposures. NIEHS-funded researchers have published work indicating prenatal vitamins might reduce the risk of having children with autism.[2] Exposure to air pollution during pregnancy and during the first year of life was also associated with autism.[3] [4] [5] NIEHS funds two key autism studies: the Childhood Autism Risks from Genetics and the Environment (CHARGE) study, and the Markers of Autism Risk in Babies-Learning Early Signs (MARBLES) study. In April 2014, NIEHS hosted a community virtual forum on autism and the environment that was webcast live and featured a panel of autism research experts.

RESEARCH UPDATE ON ENDOCRINE DISRUPTORS

NIEHS is the leading government agency funding research on the human health effects of exposure to endocrine disrupting chemicals (EDCs). EDCs have the potential to interfere with a host of physiological functions, contributing to the development of costly and devastating illnesses such as obesity, diabetes, attention deficit hyperactivity disorder (ADHD) and behavioral disorders, asthma, endometriosis and uterine fibroids, reproductive disorders and infertility, and breast, uterine, and prostate cancers. Exposures to EDCs have been documented across the population, with fetuses and young children at greater risk due to their stages of rapid development. NIEHS is currently funding over 100 grants examining effects of EDCs including bisphenol A (BPA), arsenic, pesticides, flame retardants, and others.

NIEHS has focused particular efforts on BPA, in part due to its ubiquity, that results in daily exposures for most people, mainly through diet. The Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY—BPA) research program is a collaborative effort of the NIEHS, the National Toxicology Program (NTP), the Food and Drug Administration's National Center for Toxicological Research, and academic researchers studying a range of health endpoints, while also establishing new testing standards and methodologies. A recent study of another EDC, phthalates, shows that levels of some plasticizers have fallen since a Federal ban on their use in children's products and voluntary removal from many consumer goods.[6] However, research at Brown University suggests that replacement chemicals may be just as damaging to the reproductive development of boys.[7]

RESEARCH UPDATE ON GULF OIL SPILL

The release of millions of gallons of crude oil following the 2010 Deepwater Horizon (DWH) disaster posed unpredictable risk to over 130,000 workers trained and potentially involved in various remediation activities and to the people living along the Gulf Coast. To date, there have been limited studies on the human health effects of oil spills, especially long-term effects. The NIEHS Gulf Long-term Follow-up Study (GuLF STUDY), funded in part by the NIH Common Fund, is investigating potential short- and long-term health effects associated with oil spill clean-up activities. The GuLF STUDY has enrolled 32,786 individuals and has completed home visits for 11,200 participants, during which clinical measurements were taken and biospecimens were collected for future research.

NIEHS leads the DWH Research Consortia that funds a network of academic and community partners to study health effects in people residing in regions affected by the disaster. These studies are examining resilience at the individual and community levels, perceptions of risk among women and children, and the potential contamination of seafood in the Gulf (Strategic Plan Goals 4–6). While NTP is con-

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[2] Int J Epidemiol. 2014 Feb 11. [Epub ahead of print] Maternal lifestyle and environmental risk factors for autism spectrum disorders. Lyall K1, Schmidt RJ, Hertz-Picciotto I.

[3] Epidemiology. 2014 Jan;25(1):44-7. Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. Volk HE1, Kerin T, Lurmann F, Hertz-Picciotto I, McConnell R, Campbell DB.

[4] JAMA Psychiatry. 2013 Jan;70(1):71-7. doi: 10.1001/jamapsychiatry.2013.266. Traffic-related air pollution, particulate matter, and autism. Volk HE1, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R.

[5] Autism Res. 2013 Aug;6(4):248-57. doi: 10.1002/aur.1287. Epub 2013 Mar 11. Prenatal and early-life exposure to high-level diesel exhaust particles leads to increased locomotor activity and repetitive behaviors in mice. Thirtamara Rajamani K1, Doherty-Lyons S, Bolden C, Willis D, Hoffman C, Zelikoff J, Chen LC, Gu H.

[6] Zota AR, Calafat AM, Woodruff TJ. 2014. Temporal trends in phthalate exposures: findings from the National Health and Nutrition Examination Survey, 2001–2010. Environ Health Perspect; http://www.ncbi.nlm.nih.gov/pubmed/24425099.

[7] Saffarini CM, Heger NE, Yamasaki H; Liu T, Hall SJ, Boekelheide K. 2012. Induction and persistence of abnormal testicular germ cells following gestational exposure to di-(n-butyl) phthalate in p53-null mice. J Andrology; 33(3):505–513. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3607946

ducting research to increase our understanding of the toxicology of crude oil, NIEHS grantees have preliminary results that suggest increased depression and anxiety among Gulf Coast residents, but also suggest strong community networks promote resilience.

PREPARED STATEMENT OF JOSEPHINE P. BRIGGS, M.D.

Mr. Chairman and Members of the Committee: As the Director of the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH), I am pleased to present the President's fiscal year 2015 budget request for NCCAM. The fiscal year 2015 budget includes $124,509,000, which is $384,000 more than the comparable fiscal year 2014 appropriation of $124,125,000.

The National Center for Complementary and Alternative Medicine (NCCAM) is the Federal Government's lead agency for supporting scientific research on complementary practices and integrative health interventions. NCCAM's mission is to define, through rigorous scientific investigation, the usefulness and safety of such practices and their roles in improving health and healthcare.

COMPLEMENTARY AND INTEGRATIVE HEALTH CARE

Complementary and integrative health practices are defined as having origins outside of mainstream conventional medicine and include both self-care practices like meditation, yoga, and dietary supplements, as well as healthcare provider administered care such as acupuncture, chiropractic, osteopathic and naturopathic medicine. As these modalities are increasingly integrated into mainstream healthcare, NCCAM is committed to developing the scientific evidence needed by the public, healthcare professionals and health policymakers to make informed decisions about the use and integration of these various practices.

USE OF COMPLEMENTARY AND INTEGRATIVE HEALTH CARE

For the past decade, some 30 to 40 percent of Americans have used complementary and integrative health practices, according to data from the National Health Interview Survey (NHIS) conducted by the Centers for Disease Control and Prevention (CDC). The NHIS data shows that Americans are willing to pay for these services, spending some $34 billion in 2007, which represented 1.5 percent of total health expenditures and 11 percent of out-of-pocket costs. NCCAM has worked with the CDC since 2002, to develop the questions on complementary healthcare that are included in the NHIS every 5 years (2002, 2007, and 2012). Results from the latest survey are currently being analyzed for publication later this spring. Analysis will include, for the first time, a comparison of regional variations in use of complementary health practices by adults in the United States. We also look forward to the first detailed look at integration of complementary interventions into private medical practice when the results of the 2012 National Ambulatory Medical Care Survey, which involved interviews of 30,000 physicians, are analyzed. NCCAM worked closely with the CDC to develop the questions used in this survey, as well.

IMPACT ON PUBLIC HEALTH

NCCAM's approach to setting priorities and investment in research is guided by the need for rigorous evidence that ultimately may have a significant impact on public health. One example of this approach involves a major clinical trial supported jointly by NCCAM and the National Heart, Lung, and Blood Institute examining the efficacy of using EDTA-based chelation therapy to reduce cardiovascular disease and prevent heart attacks. The trial, which involved 1,700 patients, showed a modest reduction in cardiovascular events for adults aged 50 and older who had suffered a prior heart attack. However, the results from a secondary analysis of the trial data suggest that the chelation treatments produced a marked reduction in cardiovascular events and death in patients with diabetes but not in those without diabetes. Addressing cardiovascular disease in diabetics is an important public health challenge, and better treatment options are required. As this study was not designed to discover how or why chelation might benefit patients with diabetes, further investigation is needed. Thus, NCCAM is exploring the possibility of a follow-up study in collaboration with several other NIH Institutes.

REDUCING PAIN AND IMPROVING SYMPTOM MANAGEMENT

According to the Institute of Medicine, pain is a major public health problem affecting more than 100 million Americans and costing the Nation over $600 billion

in medical costs and lost productivity. Pain is also the most common reason Americans turn to complementary and integrative health practices, as conventional medicine often provides incomplete relief. Therefore, pain research is a top priority for NCCAM. As such, we continue to invest in research on several promising approaches for treating pain, such as spinal manipulation, massage, yoga, meditation, and acupuncture. We are particularly interested in understanding how these interventions work, for what type of pain condition, and for determining the optimal method of practice and delivery. Toward this end, NCCAM partners with others in supporting research initiatives, participates in the NIH Pain Consortium, and leads an NIH Task Force to improve standards for research on chronic low back pain (cLBP). The cLBP Task Force has developed common standards, measures, and other tools for clinical research on cLBP, and a report is expected to be published in The Journal of Pain later this year.

Another important collaborative effort is our partnership with the National Institute on Drug Abuse and the Department of Veterans Affairs to foster research on complementary and integrative approaches to managing pain and other symptoms experienced by military personnel and veterans. A number of grant applications were submitted in response to our joint solicitation, and we anticipate funding multiple studies later this fall.

One area of particular interest is the means by which complementary health practices affect the perception of pain by the brain. Specifically, we seek to understand the mechanisms by which emotions, attention, and context modulate pain. Using neuroimaging and cutting-edge technologies, our intramural research program (IRP) is exploring the central mechanisms of pain and its modulation, with the long-term goal of improving clinical management of chronic pain through the integration of pharmacological and non-pharmacological complementary health approaches. NCCAM's IRP engages and leverages the exceptional basic and clinical neuroscience efforts across NIH.

ADVANCING RESEARCH ON NATURAL PRODUCTS

Another important area of emphasis for NCCAM is research on natural products. In addition to exploring the underlying biological effects and mechanisms of natural products, such as dietary supplements, herbs, botanicals, and probiotics, we are concerned about their safety. While there is widespread use of these products by the public, there is limited scientific evidence about their effectiveness and safety. In addition to gaining greater understanding of whether natural products are effective or safe when used alone, there is a need to study how they interact with prescription medications. This is very important because many patients taking prescription medications also use natural products, such as dietary supplements, herbs and probiotics. To investigate these issues, NCCAM will launch an initiative to develop rigorous methods to evaluate potential interactions between natural products and medications. The ultimate goal is to ensure that consumers, healthcare providers, and health policymakers are better informed of the potential risks and/or benefits associated with the use of natural products in combination with medications.

To propel needed innovations in technology and methodology for research on natural products, NCCAM and the NIH Office of Dietary Supplements are supporting the establishment of a Center for Advancing Natural Products Technology and Innovation. The Center is expected to better support the needs of the natural products community while reducing resource redundancies.

PROVIDING USEFUL INFORMATION TO THE PUBLIC

NCCAM provides objective, evidence-based information to scientists, healthcare providers, and the general public through a variety of approaches, including emerging technology and platforms (i.e., video, social media, and mobile applications) and an information-rich Web site (www.nccam.nih.gov). Through these approaches, science-based information on the safety and efficacy of complementary and integrative health practices—already in wide public use—is made available to a broad audience.

CONCLUSION

NCCAM continues to support research, collaborate with others, and leverage partnerships to build the scientific evidence needed by consumers, healthcare professionals, and health policymakers regarding the safety and value of complementary and integrative health practices.

PREPARED STATEMENT OF ROGER I. GLASS, M.D., PH.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the Fogarty International Center (FIC) of the National Institutes of Health (NIH). The fiscal year 2015 FIC budget of $67.776 million includes an increase of $0.292 million more than the fiscal year 2014 enacted level of $67.484 million.

The United States and the NIH have historically been at the forefront of major scientific discoveries that have improved health here at home and around the world. Building on these successes, ambitious health targets for the future now seem possible—such as a decrease in the overall mortality rate of children under the age of 5, to 20 deaths per 1,000 over the next two decades and an AIDS-free generation. Reductions in morbidity and mortality from non-communicable diseases have also begun to affect populations worldwide. At this critical juncture, the Fogarty International Center mission and investments will continue to accelerate the pace and progress of research, engage the best and brightest minds by building capacity at research institutions across the globe, and develop the evidence needed to confront health challenges wherever they occur. By continuing to invest in training outstanding early-career investigators and developing future global health research leaders, Fogarty will advance the goals and sustain the leadership of the NIH and the U.S. Government in biomedical research, while improving the health of Americans and populations worldwide.

TODAY'S BASIC SCIENCE FOR TOMORROW'S BREAKTHROUGHS

Non-communicable diseases and disorders (NCDs) are rapidly becoming the dominant causes of poor health in all low and middle-income country (LMIC) regions [1] except sub-Saharan Africa, where they are second only to HIV/AIDS. For example, World Health Organization data suggest that one billion people worldwide suffer from some type of mental, neurological or substance abuse disorder.

In collaboration with eight NIH Institutes and Centers (ICs), Fogarty's Brain Disorders in the Developing World: Research Across the Lifespan program supports cutting-edge basic science research in LMICs on the nervous system. This research could lead to important new diagnostics, prevention and treatment strategies, and interventions of direct relevance to both LMIC and U.S. populations. For example, Argentinian scientists, in collaboration with Northwestern University, are studying neuroprotective gene therapy in a preclinical trial. This team demonstrated that a unique vector gene delivery system using two powerful neuroprotective molecules could be effectively injected over time restoring neuronal function. Future studies will use magnetic nanoparticles to perform targeted gene therapy with the goal of treating neurodegenerative disease such as Parkinson's, the second-most common neurological disease in the United States, affecting approximately 1 million Americans (National Parkinson Foundation).

NURTURING TALENT AND INNOVATION

Fogarty programs have supported long-term research training for more than 4,500 scientists worldwide, in collaboration with more than 230 U.S. and LMIC research institutions. These investments provide unique training opportunities for early-career global health researchers, enabling them to effectively collaborate with foreign partners in diverse, low-resource international settings to confront global health challenges. Fogarty supports these hands-on, clinical research training experiences in LMICs in close partnership with a number of NIH ICs, providing experiences that encourage U.S. investigators to creatively approach problems under constraints that may not exist in high-income settings. Scientists trained with Fogarty support have conducted research on cardiovascular disease in Kenya, surgical capacity in Rwanda, mental health impacts of slum-dwelling in India, and the link between breast cancer and osteoporosis in China.

Solving many of today's complex public health problems requires the engagement of investigators from a wide variety of fields. Fogarty's Framework Programs for Global Health Innovation awards support efforts to bring biomedical scientists together with students from various disciplines— such as engineering, nutrition, business, law, environmental science, social sciences, agriculture and public health—to develop research training initiatives that encourage innovative, health-related products, processes and policies. This program supports: scientists at Michigan State

[1] LMIC is a World Bank designation for the classification of economies, based on Gross National Income (GNI) per capita. Low income countries have a GNI per capita of $1,035 or less, and middle income countries have a GNI per capita of $1,036–$12,615.

University studying interactions between agriculture, water resource utilization and malaria in Malawi; grantees at Northwestern University, Chicago, and the University of Cape Town, South Africa training researchers in developing healthcare technologies in Nigeria; and scientists at Tufts University School of Medicine, Boston, and Christian Medical College, Vellore, India developing a training program in translational research related to non-communicable and infectious diseases. These international teams are identifying critical health needs and conducting the research needed to develop and test novel solutions.

THE PATH FORWARD: ADDRESSING DUAL BURDENS OF DISEASE AND HARNESSING THE INFORMATION AND COMMUNICATION TECHNOLOGY REVOLUTION FOR GLOBAL HEALTH RESEARCH

For over 25 years, Fogarty has contributed to the U.S. Government fight against HIV, training and supporting some of the world's foremost vaccine and biomedical researchers. As the global burden of disease shifts to a greater level of NCDs, Fogarty programs will continue critical work in HIV research training while also responding to both the NCD epidemic through research and training programs and the nexus between the HIV and NCD epidemics, represented by NCD co-morbidities of HIV infection and treatment. As scientific priorities evolve to match the changing burden of disease, Fogarty research and research training programs will train the best and brightest researchers around the world and facilitate scientific collaboration that meets new priorities while building on existing capacity and infrastructure.

The information and communication technology (ICT) revolution presents exceptional opportunities and new tools for global health research and research education. ICT is a broad term that encompasses communication devices, applications, and services, such as cell phones, computers, radios, videoconferencing and distance learning. Fogarty will expand its support of innovation in the use of ICT to generate knowledge, scientific exchange, and research education in the hope of stimulating the capacity to develop and evaluate different models of distance learning and other ICT strategies, as well as adapt various ICT platforms for the needs of research and research educational communities. This will enable professionals in LMIC institutions to determine what works best for their particular settings as they develop novel education tools. Students and faculty will access, teach, and share information in creative and transformative ways, enabling new approaches to collaborative learning and problem solving in partnership with colleagues next door and across continents.

The enormous potential for mobile technology to impact healthcare and research has led to the rapid development of new health-related phone applications. Rigorous evaluation of health outcomes after implementation of these interventions are often lacking. New emphases are being pursued to develop mobile technologies tailored to LMIC settings, assess their impact on health and determine how they can be effectively scaled up in diverse, low-resource settings. Significantly, this evidence base is not only critical for LMIC populations, but can also be applied to healthcare in the U.S.

These are indeed exciting times for global health with new opportunities for partnership within and outside the NIH, the introduction of transformative technologies and mutual scientific priorities based on a shared burden of disease across high-income and LMIC. Capitalizing on these developments demands a multidisciplinary research workforce that can function across cultures and borders to solve common health problems. Fogarty will continue to invest in training the next generation of leaders in global health research at home and abroad to ensure that the U.S. will continue to play a key role in confronting the global health challenges of today.

PREPARED STATEMENT OF PATRICIA A. GRADY, PH.D., RN, FAAN

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2015 budget request for the National Institute of Nursing Research (NINR) of the National Institutes of Health (NIH). The fiscal year 2015 NINR budget is $140,452,000 which is $128,000 more than the comparable fiscal year 2014 appropriation of $140,324,000.

I appreciate the opportunity to share with you a brief summary of some of the exciting areas of research and future scientific directions of NINR. The mission of NINR is to promote and improve the health of individuals, families, and communities. We fulfill this mission by supporting clinical and basic research to build the scientific foundation for clinical practice, prevent disease and disability, manage and eliminate symptoms caused by illness, enhance end-of-life and palliative care, and

train the next generation of nurse scientists. Today, I offer an overview of NINR's efforts and accomplishments in five key scientific areas and provide examples of how the research we support improves quality of life, health, and wellness across the lifespan.

SYMPTOM SCIENCE: PROMOTING PERSONALIZED HEALTH STRATEGIES

NINR is committed to finding new and better ways to treat the symptoms of chronic and acute illnesses which can cause significant suffering for individuals and families. While we still have much to learn about the unique ways people experience symptoms and respond to treatments, recent advances in genomics are providing new opportunities to develop improved, personalized strategies to address adverse symptoms of illness, such as pain, fatigue, and disordered sleep. By providing a better understanding of the basic underlying biological and genetic mechanisms of symptoms, NINR-supported researchers are making important contributions to improving health and quality of life. For example, one NINR-supported project found that, for pregnant women with depression, poor sleep was associated with higher levels of inflammatory chemicals in the body known as cytokines, as well as adverse pregnancy outcomes such as preterm birth. Other NINR-supported scientists identified pro- and anti-inflammatory biomarkers that predict how patients experience pain at different stages of breast cancer treatment, drawing a new link between pain and inflammation. Discoveries such as these pave the way for the development of personalized and effective treatments for adverse symptoms of illness.

SELF-MANAGEMENT OF CHRONIC ILLNESS

According to the Centers for Disease Control (CDC), chronic illness accounts for more than 75 percent of healthcare costs in the U.S., and often requires long-term management of illness among individuals, families, and healthcare providers. Learning how to manage chronic illness presents challenges to individuals of any age as well as their family members, from children remembering to bring their asthma medication with them to school to older adults maintaining daily activities as they face multiple chronic conditions, such as arthritis and heart disease. To address such challenges, NINR supports research that enables individuals with chronic illness and their caregivers to take an active role in understanding and managing their condition, and improving their quality of life. One current NINR-led initiative aims to equip families with effective strategies for improving self-management of chronic illness in children and adolescents, enabling them to follow treatment regimens and make healthy lifestyle choices while still allowing "kids to be kids." Another initiative emphasizes family-centered self-management that integrates family members as partners in care while promoting self-management for individuals of any age; this initiative has the potential to strengthen the ability of family members to work together to make treatment decisions, manage symptoms, and navigate the healthcare system. Through efforts like these, NINR's investment in self-management research contributes to helping people live active and healthy lives in the face of chronic illness.

WELLNESS: PROMOTING HEALTH AND PREVENTING ILLNESS

Another area of emphasis at NINR is on wellness research, which seeks to understand the physical, social, behavioral, and environmental causes of illness, identify healthy lifestyle behaviors, and develop interventions to promote health and prevent illness across the lifespan and in diverse communities. One study supported by NINR is refining and examining the effectiveness of a home-based sensor system for older adults, which monitors pulse, breathing, and restlessness while sleeping, and alerts healthcare providers to potential illness so that they can intervene early. Such warning systems may allow older adults to stay active and remain in their homes longer. In another project, researchers developed a teacher-delivered healthy lifestyles intervention that improved health behaviors and academic outcomes in high school adolescents. NINR also maintains its commitment to promoting wellness in vulnerable groups who are disproportionately affected by chronic illness. We currently lead an initiative to reduce health disparities in minority and underserved children through the development of culturally-appropriate, multifaceted interventions.

ENHANCING END-OF-LIFE AND PALLIATIVE CARE

Addressing the needs of patients with life-limiting illness through high-quality, effective end-of-life and palliative care continues to be a critical focus of NINR. As the lead NIH Institute for end-of-life research, NINR supports research to ease symp-

toms and support patients and their caregivers in coping with advanced illness, while also addressing the challenges of planning for end-of-life decisions. As an example, NINR-supported scientists recently found that pain continues to be underdiagnosed and undertreated for hospitalized patients at the end of life, suggesting that more work is needed to better understand the needs of individuals facing life-threatening illnesses. Recognizing that palliative care is a critical component of maintaining quality of life at any age and at any stage of illness, not just at the end of life, NINR supports initiatives to enhance palliative care. Given that a diagnosis of serious illness in a child is particularly difficult for families, NINR launched the Palliative Care: Conversations Matter™ campaign to raise awareness of pediatric palliative care and to provide evidence-based materials to help healthcare providers initiate often difficult conversations with pediatric patients and their families. NINR also continues to support a palliative care research cooperative to enhance the evidence base for palliative care interventions. A new NINR initiative to promote use of and long-term sustainability of the cooperative will encourage researchers across the country to capitalize on the existing resources and expertise and streamline the research process.

LOOKING TOWARD THE FUTURE: NURSE SCIENTISTS

A primary goal of NINR is to prepare the next generation of nurse scientists to address health challenges and to contribute to an innovative, multidisciplinary, and diverse scientific workforce. NINR funds training and career development grants and programs to prepare nurse scientists to conduct research to build the scientific foundation for clinical practice. NINR's Summer Genetics Institute is an intensive training program on molecular genetics designed to improve research and clinical practice among graduate students and faculty. This year, our week-long Methodologies Boot Camp focuses on using Big Data in symptom research, and provides a research intensive program for participants to learn new state-of-the-art methodologies from nationally and internationally known scientists. By training nurse scientists to use new, innovative scientific methodologies, NINR advances nursing science to improve health.

In closing, thank you for the opportunity to share with the Committee some of the ways the science we support impacts the health of the Nation. In fiscal year 2015, NINR will continue our mission to improve quality of life by advancing nursing science and by supporting research to inform high-quality and effective clinical care.

PREPARED STATEMENT OF ERIC GREEN, M.D., PH.D

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2015 President's budget request for the National Human Genome Research Institute (NHGRI). The fiscal year 2015 budget of $498,451,000 reflects an increase of $1,323,000 above the enacted fiscal year 2014 level of $497,128,000.

The research funded and conducted by NHGRI in fiscal year 2015 will continue to unlock the secrets of life's DNA code. We still have much to discover with regard to how the three billion DNA bases of the human genome influence our physical and biochemical characteristics—and, in turn, our health. While we continue to reveal all the information encoded by DNA, we have started pursuing clinical applications of genomic knowledge and implementing genomic medicine.

Understanding how the structure and function of the human genome relates to health and disease will be essential for the implementation of genomic medicine. Among the knowledge to be gained is how the ~20,000 genes in the human genome are turned on and off at the appropriate times and in the appropriate places; this is largely the role of regulatory elements within the genome that act like "dimmer switches" controlling lights. Through the Institute's Encyclopedia of DNA Elements (ENCODE) Project, a more detailed inventory of these regulatory elements is emerging. In fiscal year 2015, the Genomics of Gene Regulation (GGR) initiative will begin to investigate the choreography of these different elements in different cells and tissues. Many of the elements that ENCODE has identified and GGR will characterize play a role in human diseases and traits, underscoring the foundational value of these projects.

More than 25 million Americans suffer from rare diseases, cumulatively more than those afflicted with cancer. While the genomic bases for just over 5,000 rare diseases have been established—the majority of those established since the end of the Human Genome Project—the causal genes for an estimated 2,000–4,000 additional rare diseases remain to be identified. To investigate the latter, NHGRI's Centers for Mendelian Genomics Program is harnessing powerful DNA-sequencing tech-

nologies to analyze patients' genomes on an unprecedented scale en route to establishing the genomic underpinnings of these remaining rare disorders. The resulting discoveries offer the promise of ending the diagnostic odyssey of afflicted patients as well as insights about the diseases that may lead to new therapeutic approaches.

In fiscal year 2015, NHGRI will also focus on more common, but more genomically complex, diseases—those diseases that reflect great public health burdens. One such disease, cancer, is fundamentally a disease of the genome. Hence, NHGRI has been collaborating with the National Cancer Institute in developing The Cancer Genome Atlas (TCGA) since 2006, studying the genomes of different types of tumors and cataloging the discovered genomic aberrations. In fiscal year 2015, TCGA will reach the milestone of analyzing 10,000 tumor samples, revealing many new insights about cancer.

Similarly, NHGRI has partnered with the National Institute on Aging to pursue the largest genomics study of Alzheimer's disease to date. The Alzheimer's Disease Sequencing Project (ADSP) is sequencing and analyzing the genomes of several hundred Alzheimer's patients to help identify the genomic factors contributing to this complex disease, which affects as many as 5 million Americans aged 65 and older.

Investigators throughout the biomedical research enterprise—well beyond the study of genetic diseases—are now incorporating genomic analyses into their research. A major catalyst for this dissemination has been NHGRI's unparalleled Advanced DNA Sequencing Technology Program, the successes of which have led to a phenomenal drop in the cost of DNA sequencing,[1] enabling many more investigators to incorporate genomic analyses into their research. However, these researchers have a widespread and urgent need for improved analytical tools for analyzing DNA sequence data. To address this, NHGRI has created the Genome Sequencing Informatics Tools (GS-IT) program. Like the Institute's development of cutting-edge innovations in DNA sequencing, GS-IT is creating pioneering robust data-analysis tools for studying genomes.

To become a reality, genomic medicine needs refined approaches for using genomic information to improve health outcomes. For instance, in fiscal year 2015, the Implementing Genomics Into Clinical Practice (IGNITE) Network will test methods for disseminating genomic medicine strategies more widely. IGNITE investigators will be initially studying the use of genomic risk information for treating kidney disease, the utility of family health history, and the use of genomic information for selecting appropriate medications. In another effort, NHGRI is partnering with the Eunice Kennedy Shriver National Institute of Child Health and Human Development to support the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) Program, which is examining the potential for genome sequencing to improve the care of newborns.

Pilot programs such as IGNITE and NSIGHT, in addition to other large genomics projects, are only valuable if the generated knowledge diffuses through the medical establishment. To help healthcare professionals become competent with genomic information in delivering patient care, NHGRI is working with the National Center for Biotechnology Information to develop the Clinical Genome Resource (ClinGen), which will provide a curated knowledgebase of clinically relevant genomic variants. ClinGen will be freely available to clinicians, researchers, and professional organizations developing clinical practice guidelines, helping to usher in larger-scale implementation of genomic medicine.

To capitalize on the genomics research funded by NHGRI and other NIH institutes for medicine, the next generation of scientists and clinicians must be equipped with the skills to lead their fields during the 21st century. In fiscal year 2015, new institutional training programs and individual career awards in genomics research and in genomic medicine will develop leaders in those respective fields, including the provision of cross-training in associated disciplines such as bioethics and data science.

Another of NHGRI's educational efforts targets the general public. The Institute collaborated with the Smithsonian Institution's National Museum of Natural History to create the exhibition Genome: Unlocking Life's Code. Privately funded, this widely acclaimed exhibition is expected to be visited by more than 3.5 million people before the end of fiscal year 2015. In addition, a series of nine public engagement programs are being produced; these events will remain accessible via the web to complement the exhibition as it travels North America over the next 5 years.

As described above, NHGRI's genome sciences portfolio will continue to explain the role of the genome in human traits and disease, while its genomic medicine portfolio will apply that knowledge to improve human health. The Institute will en-

[1] Nature 507, 294–295 (20 March 2014) http://www.nature.com/news/technology-the-1-000-genome-1.14901

sure that information about genomic advances is disseminated to scientists and healthcare professionals as well as the general public, and that the technologies and generated knowledgebase will continue to be a growth engine for our economy.[2]

PREPARED STATEMENT OF ALAN E. GUTTMACHER, M.D.

Mr. Chairman and Members of the Committee, I am pleased to present the fiscal year 2015 President's budget request for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of $1,283,487,000. This reflects an increase of $2,657,000 over the fiscal year 2014 level of $1,280,830,000.

Understanding human development, both normative and atypical, comprises the core of NICHD's mission. The Institute supports a broad range of research, conducted largely at academic institutions across the country, ranging from efforts to increase understanding of basic biological mechanisms to testing health interventions aimed at improving the lives of children, women, families, and those with disabilities. NICHD-supported research contributes to knowledge about our health, from the earliest stages through maturity.

PREGNANCY AND BIRTH OUTCOMES

Based on NICHD-supported research showing less than optimal health outcomes for infants born at 37 and 38 weeks of pregnancy (previously considered full-term), leading professional societies announced in the past year a new policy that pregnancy would now be considered full-term only after 39 weeks. This change should lead to improved standards of care and better health outcomes for mothers and infants.

While previous studies had found that alcohol and illegal drug use during pregnancy frequently produce poorer infant health outcomes, a NICHD-funded network study has now provided evidence that smoking (including secondhand smoke), prescription painkillers, and illegal drugs used during pregnancy can double or triple the risk of stillbirth. These findings provide women and their clinicians important information about healthy behaviors in pregnancy.

Through our Hunter Kelly Newborn Screening Research Program, NICHD has long provided the evidence base for determining whether a health condition can be detected in newborns, and whether it can be cured or treated. Currently, most states screen newborns for a panel of 29 conditions, thus preventing extensive disease and disability. Now NICHD is partnering with the National Human Genome Research Institute on a major study to explore the possibilities for early diagnosis of a much larger number of disorders by sequencing newborns' genomes, while also exploring technical, clinical, and ethical questions raised by this new technology. Researchers also plan to develop a tool to help parents understand sequencing results, placing special emphasis on the needs of families from diverse cultures and their clinicians.

PEDIATRIC AND ADOLESCENT DEVELOPMENT

For many conditions, the earlier they are identified and treatment begun, the better the outcome. One of the goals of the NICHD-led National Children's Study is to amass an unprecedented amount of information about children's health, development, and environment to understand and improve health. Recently, researchers supported by NICHD have developed an updated screening tool, administered to parents, to help determine if a child between 18 months and 2 years old has autism, much earlier than the current average age of diagnosis of 4 years. Previous research has shown that earlier interventions can help improve developmental outcomes for children with autism. This tool is now widely available online, in 45 different languages.

Since variations in nutrition and environment so heavily influence children's growth and development, NICHD engages in international studies to increase knowledge about optimal health in childhood. In some nutrient-deficient areas, children receive iron supplements to enhance development and prevent anemia; yet, recently, public health officials have become concerned that these supplements may increase children's risk for malaria. To test this theory, NICHD-supported researchers conducted a randomized clinical trial combining iron supplementation with prevention efforts (such as sleeping nets) in a malaria-prone area of Ghana, finding that the incidence of malaria was no higher for children who received the supple-

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[2] http://www.unitedformedicalresearch.com/advocacy__reports/the-impact-of-genomics-on-the-u-s-economy/

ments than for those who did not, and assuring that beneficial iron supplementation could continue.

Understanding human development in adolescence, with that period's substantial physical, mental, and behavioral changes, poses a particular challenge for researchers. While there is increased emphasis on encouraging young people to be physically active to reduce overweight and increase health, engaging in some physical activities may pose risks. Concerns have been raised about the potential long-term effects of repeated concussions in children, especially young athletes. Recently, NICHD partnered with other NIH ICs and the National Football League on eight research projects to help understand the effects of head injuries and improve the diagnosis of concussions. Although awareness is increasing that young people who may have had a concussion should not immediately return to play, these studies will help us understand the brain's healing process and what is required to prevent permanent damage to this vital organ, leading to such advances as more precise return to play policies.

Parents of teenagers will not be surprised that adolescents often engage in risk-taking behaviors. They may, however, be surprised that informed parental supervision can have an impact on adolescent behaviors and even on potential injury or death. An intramural NICHD study on teen driving behaviors collected data from a nationally representative sample of 10th graders, finding that adolescents who reported being exposed to riding with an intoxicated driver in the 10th grade were considerably more likely to report driving while intoxicated in the 12th grade. The study indicates the importance of parents' not only monitoring their own children's driving behaviors, but also that of other young drivers with whom their children may be riding.

WOMEN'S HEALTH

One result of NICHD's 2012 "Scientific Visioning" process, which took a fresh look at what the Institute might accomplish across its broad mission over the next decade, was the establishment of the new extramural Gynecologic Health and Disease Branch. Researchers supported by the branch recently shed light on the relative success and safety of two surgical treatments for pelvic organ prolapse (a form of pelvic hernia). Previous research supported by NICHD suggested about 3 percent of U.S. women experience prolapse in a given year, most commonly older women and those who have given birth several times. The study found no statistically significant difference between the two types of surgery, providing critical information for surgeons and the 300,000 U.S. women who have this surgery each year.

INDIVIDUALS WITH SPECIAL NEEDS

NICHD has long supported research on the causes and effects of intellectual and developmental disabilities, and on identifying effective therapies for these conditions. By working closely with leading researchers, clinicians, self-advocates, and families, Institute scientists identify the scientific resources most critical to ongoing progress on these conditions. In September 2013, NICHD, with the support of the NIH Down Syndrome Working Group and the Down Syndrome Consortium, launched DS-Connect™: The Down Syndrome Registry. DS-Connect™, which already includes over 1,500 registrants, is a web-based, voluntary, secure health registry serving the Down syndrome community, providing anonymized information to families and clinicians, and facilitating connections between researchers and potential clinical research participants. In addition, the Down syndrome community recently provided extensive input on a revised NIH Research Plan on Down Syndrome, which will be available mid-2014.

Another pressing need for scientists conducting research on cognition and brain disorders is the availability of sufficient brain tissue specimens. While NIH historically has funded investigator-initiated, disease-specific brain banks, it is now taking a new approach to providing these scarce research resources by supporting a tissue-sharing collaboration among five brain banks. This new "NeuroBioBank" will increase availability of biospecimens and establish a standardized resource for the research community.

EMBRACING RESEARCH OPPORTUNITIES

Increasingly, biomedical and biobehavioral researchers need to work in transdisciplinary teams, manage massive amounts of data, and acquire new and diverse skill sets. For example, the medical rehabilitation needs of those with physical disabilities require a wide range of research, from improving our understanding of neurological repair to developing new generations of prostheses and assistive devices. In 2012, a Blue Ribbon Panel made a series of recommendations to NICHD

to bolster rehabilitation research at NICHD's National Center for Medical Rehabilitation Research (NCMRR) and across NIH. NICHD is implementing an innovative new operating model for NCMRR that is intended to greatly increase coordination of rehabilitation research among the many ICs that support it.

NICHD is excited to launch the Human Placenta Project, a coordinated international initiative to understand in real time the structure and function of the human placenta, arguably the least understood human organ. The placenta is not only critical for both maternal and fetal health, but also has substantial implications for conditions that arise later in life in both the mother and child, such as cardiovascular disease. The Project's goals include understanding placental development in normal and abnormal pregnancies, developing biomarkers to help predict adverse pregnancy outcomes, and developing interventions to prevent abnormal placental and fetal development. The currently projected span of the project is a decade, beginning with a workshop in May 2014 to develop a research plan.

Thank you for the opportunity to submit some of NICHD's accomplishments over the last year and a few of its many exciting plans for the immediate future.

PREPARED STATEMENT OF RICHARD J. HODES, M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2015 budget request for the National Institute on Aging (NIA) of the National Institutes of Health (NIH). The fiscal year 2015 budget includes $1,170,880,000, which is $1,453,000 more than the comparable fiscal year 2014 level of $1,169,427,000.

More than 40 million people age 65 and older live in the United States, and data from the Federal Interagency Forum on Aging-Related Statistics indicate that their numbers will double by 2040. In less than 50 years, the number of "oldest old"—people ages 85 and older—may quadruple. As record numbers of Americans reach retirement age and beyond, profound changes will occur in our economic, healthcare, and social systems.

The NIA leads the national effort to understand aging and to develop interventions that will help older adults enjoy robust health and independence, and continue to make positive contributions to their families and communities. We support genetic, biological, clinical, behavioral, and social research related to the aging process, healthy aging, and diseases and conditions that often increase with age. We also support training of the next generation of researchers.

UNDERSTANDING AGING AT ITS MOST BASIC LEVEL

NIA-supported studies in the emerging field of geroscience, which explores the basic mechanisms underlying age-related changes, including those which could lead to increased disease susceptibility, will provide needed insight into ways to address aging-related diseases and disorders. The NIA-led NIH GeroScience Interest Group (GSIG) involves active participation by 20 NIH Institutes and is leading the effort to accelerate and coordinate efforts to promote further discoveries on the common risks and mechanisms behind age-related diseases and conditions. In October 2013, the GSIG and private-sector partners convened a national Summit, "Advances in Geroscience: Impact on Healthspan and Chronic Disease," which drew more than 500 expert participants from around the world. We expect its outcomes to further energize this field.

An increasingly important research area is the identification of genes and gene variants related to aging and age-related disease. Such research will be accelerated by the addition of data on more than 78,000 older individuals from one of the Nation's largest and most diverse genomics projects, Genetic Epidemiology Research on Aging, to the NIH database of Genotypes and Phenotypes (dbGAP). These data will be widely available to qualified investigators.

IMPROVING THE HEALTH AND WELL-BEING OF OLDER AMERICANS

NIH-supported investigators are testing a variety of interventions for health conditions common to old age. Ongoing studies include: the ASPirin in Reducing Events in the Elderly (ASPREE) trial, designed to determine whether the benefits of aspirin outweigh the risks in people over 70; testosterone supplementation to delay or prevent frailty in older men; exercise for mood, health, and cognition; and an array of interventions for menopausal symptoms.

NIA also supports research aimed at development of interventions that will enable older adults to remain independent for as long as possible. For example, researchers used data from nine large NIA-funded studies to develop diagnostic cri-

teria for low muscle mass and weakness. These conditions lead to disability in older people, but are rarely recognized as clinical problems by healthcare providers. This work is a milestone toward the development of new diagnostic and treatment strategies for this common and disabling condition. In addition, the recent NIA-supported finding that training to improve cognitive abilities in healthy older people lasts to some degree for 10 years after the training program was completed provides an important piece of evidence that cognitive health can be improved and maintained into older age.

Serious injuries from falls, such as broken bones or traumatic brain injury, are a major reason for the loss of independence among older people. In 2013, NIA and the Patient-Centered Outcomes Research Initiative (PCORI) solicited applications for funding to conduct a randomized clinical trial of a multifactorial strategy for preventing serious fall-related injuries among non-institutionalized older people. The trial will begin in 2014.

NIA is also a leader in the trans-NIH Science of Behavior Change initiative. We are hoping that the long-term outcome of this initiative will be to enhance the efficacy of interventions to help individuals make and maintain positive changes in their health behaviors. As an example, one NIA-managed study in this initiative has shed light on how stress can reduce or eliminate the ability of individuals to benefit from training designed to help them regulate their emotions and better control their behavior, suggesting possible changes to our behavioral intervention strategies.

Because investigators often, for a variety of reasons, have difficulty recruiting older people into clinical research studies, NIA is collaborating with the Administration for Community Living, the Centers for Disease Control and Prevention, state and community-based health and social service providers, researchers, and private organizations on the Recruiting Older Adults into Research (ROAR) project.

BUILDING MOMENTUM AGAINST ALZHEIMER'S DISEASE

NIA is the lead Federal agency supporting research on Alzheimer's disease (AD), which despite our best efforts continues to be a serious public health issue that directly affects as many as 5 million Americans. In fiscal year 2014, NIA received approximately $100 million in additional appropriated funds. We plan to use these additional funds to support Alzheimer's research in areas of strategic priority, funding additional awards to applications received from Funding Opportunity Announcements issued in fiscal year 2013–fiscal year 2014. We will continue to be guided by the strategic goals outlined in the National Action Plan on Alzheimer's Disease and the results from the 2012 Alzheimer's Disease Summit. A second Summit is planned for February 2015 to update milestones and stimulate further research.

Recent findings have expanded our understanding of AD and provided insights into prevention and treatment of the disease. For example, NIA-funded researchers recently identified a molecule called REST, which is lost in the brains of patients with Alzheimer's disease, and whose deletion in mice leads to neurodegeneration. REST represents a novel potential target for intervention into the disease. Investigators have also found that conjugated equine estrogens, the most common type of postmenopausal hormone therapy in the United States, has no long-term risk or benefit to cognitive function in younger postmenopausal women, aged 50–55. The earlier Women's Health Initiative Memory Study linked the same type of hormone therapy to cognitive decline and dementia in older postmenopausal women, but this finding suggests that women taking certain estrogen-based hormone therapies in their early postmenopausal years may not be at increased risk for eventual cognitive decline.

EMPOWERING THE NEXT GENERATION OF RESEARCHERS IN AGING

As the number of older Americans continues to grow, we must not only increase the number of practicing physicians trained in geriatrics and relevant subspecialties but also foster the development of the next generation of physician-scientists whose clinical research will lead to improved care and more effective treatment options for older patients with complex medical conditions. Two ongoing programs—Grants for Early Medical/Surgical Subspecialists' Transition to Aging Research (GEMSSTAR), supporting physicians who seek to become clinician-scientists in geriatric aspects of their subspecialty, and Medical Students Training in Aging Research (MSTAR), targeting first-year medical students in order to stimulate early interest in an aging research career—remain highly successful. Building on new technologies that enable us to reach a wide audience efficiently and inexpensively, we have initiated a series of Technical Assistance webinars to provide participants, particularly those with an interest in health disparities research, with guidance on navigating the NIA grants application process. Finally, the Butler-Williams Scholars Program (formerly the

NIA Summer Institute) remains a vibrant and vital institution at NIA, drawing a record number of applications for the 2014 session.

PREPARED STATEMENT OF STEPHEN I. KATZ, M.D., PH.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH). The fiscal year 2015 NIAMS budget of $520.189 million includes an increase of $0.851 million over the comparable fiscal year 2014 level of $519.338 million.

The NIAMS supports a broad range of research, training, and information dissemination activities. Many of the conditions within the NIAMS mission are very common while some are rare, affecting only a few thousand people world-wide. All have a major impact on the quality of people's lives. Diseases addressed by NIAMS affect individuals of all ages and of all racial and ethnic backgrounds; many disproportionately affect women and minorities. Over the years, NIAMS-funded research teams have made significant progress in uncovering the causes of and improving the treatments for many disorders of the bones, muscles, joints, and skin.

While many treatments for arthritis and musculoskeletal and skin conditions have their origins in NIH-supported basic research, the timeframes for translating fundamental knowledge into therapies remain unacceptably long, and too many potential therapies fail late in development. To improve the drug development process, NIAMS has partnered with industry, non-profit groups, and other government agencies for the NIH Accelerating Medicines Partnership program in lupus and rheumatoid arthritis (RA). Through the program, a network of investigators will use advanced tools and techniques to analyze blood and tissue samples from patients. The overall goals are to gain insights into lupus and RA biology, improve the selection of biological targets for drug development, and ultimately produce new therapies.

The advent of technologies for collecting and analyzing large amounts of data corresponds with an increasing appreciation of the interactions that occur among different tissues and organ systems, and with the microorganisms inside our body or on our skin. When researchers compared the gut microbes of people who had newly diagnosed, untreated RA with those found in the digestive tracts of healthy people, patients with RA who were receiving treatment, and psoriatic arthritis patients, they found that the bacterium Prevotella copri (P. copri) was more abundant in patients with new-onset RA than in the other groups. If additional studies determine that altered levels of P. copri contribute to RA, therapies that target the bacterium could help to prevent the disease or delay its onset. Similarly, another group of researchers recently demonstrated that Staphylococcus aureus colonies on the skin of people who have atopic dermatitis, or eczema, release a toxin that causes skin inflammation. This finding provides an impetus for further studies into whether blocking the toxin could help people who are susceptible to atopic dermatitis.

Other research is uncovering complex connections between the immune system and skeletal health, and the role of hormones produced by bone on the development and function of the nervous system. Recent findings have linked the misfolding of a protein that helps immune cells recognize and destroy invading bacteria or viruses to the bone erosion that characterizes spondyloarthritis of the spine. Other research has revealed that the bone-derived hormone osteocalcin is capable of interacting with neurons in the brain and influencing brain structure and behavior, at least in mice.

Many people think of broken bones as a normal part of an active, healthy childhood. Although any bone will break if enough force is applied to it, researchers are learning that the bones of some children and teens have structural deficits that can be readily identified based on what the patient was doing when the bone was broken. Children who broke an arm because of moderate impact, as would occur when falling off a bicycle, had bones that resembled their uninjured peers; but, those whose forearm bones broke upon mild impact (e.g., a fall during a minor playground scuffle) showed signs of compromised bone strength and bone quality. While we do not know the extent to which bone weakness during childhood predisposes people to osteoporosis and fragility fractures later in life, this study is the first to suggest that a simple screening question could identify the young people who might benefit most from dietary changes and activities to improve bone health.

NIAMS also is involved in efforts to identify laboratory-based or imaging biomarkers that will guide treatment development or will improve patient care. Activities include the Foundation for the NIH (FNIH) Biomarkers Consortium project to evaluate biochemical and imaging biomarkers for more precise ways of measuring osteoarthritis progression during clinical trials; this project builds on resources cre-

ated by the Osteoarthritis Initiative (OAI), a public-private partnership spearheaded by NIAMS and the National Institute on Aging with support from other NIH components, the U.S. Food and Drug Administration, the FNIH, and private sponsors. A separate research team, focused on molecular changes associated with scleroderma, recently reported that blood levels of a protein appeared to distinguish between patients who were likely to develop life-threatening lung complications that require aggressive treatments and those whose disease would not warrant risky therapies. Investigators are confirming their observations as a next step before the findings are applied clinically.

Additional research into disease-associated genetic defects and molecular pathways is pointing to new uses for drugs that have been approved for other conditions. Work by investigators studying a group of muscle diseases called the disferlinopathies—which includes limb-girdle muscular dystrophy type 2B—suggests that calcium channel blocking drugs might reduce some of the tissue damage that accumulates as the diseases progress. Another example comes from a team that identified 42 areas in the human genome that are associated with RA; many of the gene products are already targeted by existing drugs. These potential drug repurposing opportunities will be explored more thoroughly before clinical trials can begin in patients.

Once results from clinical studies are available, many healthcare providers insist that findings be validated before changing how they practice medicine. The ability to verify conclusions is equally important at the basic and preclinical levels of research, particularly when results become the basis for clinical trials. In fiscal year 2015, NIAMS plans to refocus the Pilot and Feasibility Clinical Research Grants in Arthritis and Musculoskeletal and Skin Diseases program—a grant mechanism to foster early-stage clinical trials on which larger, more robust studies will be based—to emphasize the need for a strong scientific premise on which a proposed project is based.

NIAMS is committed to ensuring that well-trained basic scientists and clinical researchers are prepared to conduct cutting-edge studies related to rheumatic, musculoskeletal, and skin diseases. The Institute awards a combination of institutional training grants and individual fellowships for this purpose. NIAMS has expanded its participation in NIH training programs for fiscal year 2015 to include the Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral MD/PhD and Other Dual Doctoral Degree Fellows (F30) program. The Institute also has begun meeting with clinical or patient-oriented research career development awardees—both early in their award and as they are about to transition to independent careers—to identify challenges that they face and ways to better support them and future awardees.

As part of a commitment to communicating about NIAMS programs and research results, NIAMS has enhanced its outreach to patients, healthcare and research professionals, and the general public via social media and other activities. Building on a successful 2013 effort to ensure that the results of NIH research investments and health messages reach all Americans, NIAMS again partnered with other components of the Department of Health and Human Services and with patient advocacy groups to create a new set of health planners, titled A Year of Health, A Guide to a Healthy 2014 for You and Your Family. In the past 2 years, NIAMS received requests for these health planners from all 50 states and five U.S. territories, demonstrating a robust need for credible, research-based health information in African American, American Indian/Alaska Native/Native Hawaiian, Asian American/Pacific Islander, and Hispanic/Latino communities.

Looking to the future, we are updating the Institute's Long-Range Plan. As with the fiscal year 2010–2014 plan, the new document will inform the Institute's priority setting process while enabling the NIAMS to adapt to the rapidly changing biomedical and behavioral science landscapes. When complete, the plan will outline the Institute's perspective on research needs and opportunities within the NIAMS mission, and will serve as a resource for all who are interested in our activities.

PREPARED STATEMENT OF GEORGE KOOB, PH.D.

Mr. Chairman and Members of the Committee: As the new Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the National Institutes of Health (NIH), I am pleased to present the President's budget request for the Institute. The fiscal year 2015 NIAAA budget request of $446,017,000 reflects an increase of $606,000 over the comparable fiscal year 2014 enacted level of $445,411,000.

SCOPE OF THE PROBLEM

Excessive alcohol use has profound effects on individuals, families and communities; and the Centers for Disease Control and Prevention (CDC) estimates that excessive alcohol consumption cost the U.S. $224 billion in 2006. In 2012, nearly one quarter of the U.S. population aged 21 and older and over 15 percent of young people ages 12–20 reported binge drinking (i.e. consuming five or more drinks on a single occasion) at least once in the past month, according to the Substance Abuse and Mental Health Services Administration (SAMHSA). Binge drinking has serious acute and long term consequences—both for youth and adults. NIAAA estimates that 18 million Americans have an alcohol use disorder (AUD) and NIAAA research has established an important connection between early alcohol use and the development and severity of AUD. Of those who meet the criteria for an AUD, only about 15 percent ever seek treatment.

NIAAA RESEARCH

To reduce the considerable burden of illness and the societal costs associated with alcohol misuse, NIAAA is working to advance evidence-based prevention and treatment for alcohol problems for individuals at all stages of life, including those with co-occurring disorders. NIAAA's research portfolio is broad, ranging from studies on the underlying biological mechanisms that drive excessive drinking and the development of medications for AUD targeting these mechanisms, to studies on policies and interventions designed to reduce harm both to drinkers and those around them. NIAAA's portfolio also includes both research on the health benefits associated with moderate drinking and on the consequences of alcohol misuse, including fetal alcohol spectrum disorders (FASD), alcohol effects on the developing adolescent brain, and alcohol effects on tissue and organ damage.

NIAAA's cutting edge work in the neuroscience of alcohol effects on the brain provides not only a firm foundation for development of novel treatments for AUD but also a framework for prevention. The NIAAA portfolio focuses on the neurocircuitry changes that promote the development of AUD as well as those that convey resilience. Particularly critical are the studies of the adolescent brain and how excessive alcohol intake can delay, or permanently compromise normal development of the brain's executive and self-regulatory functions.

A key goal of NIAAA is to work with other NIH Institutes and Centers and Federal agencies to enhance integration of research on the abuse of alcohol and other substances. Notably, NIAAA co-leads the Collaborative Research on Addictions at NIH (CRAN) with the National Institute on Drug Abuse (NIDA) and the National Cancer Institute (NCI); co-chairs the Alcohol Policy and Underage Drinking Subcommittee of the HHS Behavioral Health Coordinating Council with the CDC; and collaborates with the National Institute of Mental Health (NIMH), NIDA, Department of Defense (DOD) and the Veterans Administration (VA) on the implementation of the National Research Action Plan for Improving Access to Mental Health Services for Veterans, Service Members, and Military Families.

Recognizing that medications currently available to treat AUD can be highly effective but do not work for everyone, NIAAA continues to make significant progress towards developing additional evidence based pharmacotherapies. NIAAA's Clinical Investigations Group (NCIG), established to rapidly test candidate compounds (within 12–18 months), is streamlining the medications development process for AUD. NCIG recently completed a multisite clinical trial that showed the anti-smoking medication varenicline (Chantix®) significantly reduced alcohol consumption and craving in both smokers and non-smokers with AUD. Going forward, NCIG will test both repurposed and novel compounds often working in collaboration with extramural scientists and the pharmaceutical industry. NIAAA also supports promising pharmacotherapy research outside of NCIG. In an independent study, the widely prescribed anti-seizure medication gabapentin, used to treat pain and used off-label for migraines, reduced heavy drinking and other related symptoms in alcohol dependent patients. A study to replicate the gabapentin finding within NCIG is anticipated. It is important to note that currently available medications are very effective for many, and that NIAAA is working to make clinicians and the public aware of the range of available treatment options for AUD, as well as promoting research into more effective implementation of treatment.

Given that AUD often co-occurs with other substance use and/or mental health disorders, major priorities of the Institute are to understand the complex relationships between and develop effective treatments for alcohol misuse and co-occurring disorders. For example, AUD frequently co-occurs with post-traumatic stress disorder (PTSD), thereby complicating treatment for both conditions. PTSD is prevalent among military personnel and veterans, and also among individuals who have

experienced sexual assault—a far too common occurrence on college campuses, and one often associated with excessive drinking by both perpetrators and victims. PTSD increases risk for AUD; conversely, chronic alcohol use may increase the risk for PTSD by altering the brain's ability to recover from a traumatic experience. Using an animal model of PTSD, NIAAA intramural researchers discovered that chronic alcohol exposure altered neurons in the medial prefrontal cortex region of the brain, making the animals slower to suppress a conditioned fear response. Differences in the ability to handle fear responses could help explain differences in vulnerability to PTSD among humans, and lead to new therapeutic approaches and diagnostic risk biomarkers. NIAAA also supports other promising studies on co-occurring PTSD and AUD.

The consequences of binge drinking for all ages range from acute, e.g. injuries and blackouts, to long term, e.g. severe AUD and organ damage. Recent results of NIAAA-supported research have revealed that binge drinking may be harmful in more ways than previously thought. For example, in results published this year, a single episode of binge drinking (which in the study raised the blood alcohol concentration to 0.08 g/dL, the legal limit for driving while intoxicated, within 60 minutes) increased leakage of bacterial endotoxins from the gut into the bloodstream and elicited an immune response, demonstrating that binge drinking produces acute damage in the body, even in healthy people. Notably, women had higher blood alcohol levels and circulating endotoxin levels than men. Often viewed as a rite of passage, binge drinking is pervasive among our Nations' youth with 1.7 million young people ages 12–20 engaging in this behavior five or more times per month according to SAMHSA. NIAAA's current studies on the effects of alcohol on the developing brain will inform a more extensive study under CRAN to assess the effects of drugs and alcohol, alone and in combination, on the adolescent brain. College and University Presidents are especially concerned about the rampant heavy use of alcohol among their students resulting in an estimated 1,825 deaths, 696,000 assaults, and 97,000 sexual assaults annually. NIAAA will soon release a decision tool to help college administrators select effective evidence-based interventions appropriate for their campuses. NIAAA also promotes screening and brief intervention (SBI) for youth, and launched an online course with Medscape to provide continuing medical education for healthcare professionals to help them conduct fast, evidence-based alcohol SBI with youth. To date, over 14,000 healthcare providers have been Medscape certified.

Preventing, diagnosing, and treating alcoholic liver disease (ALD) is also a major priority. NIAAA funds four research consortia to pursue new clinical approaches to treat alcoholic hepatitis, a severe form of ALD. NIAAA will also continue to pursue biomarkers of liver injury to facilitate earlier diagnosis.

NIAAA has significantly advanced our understanding of the health and social impacts of alcohol use and misuse. NIAAA will continue to pursue opportunities leading to better outcomes for alcohol-related problems, and support a diverse biomedical research workforce that is equipped to tackle these public health challenges.

PREPARED STATEMENT OF DONALD A.B. LINDBERG, M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Library of Medicine (NLM) of the National Institutes of Health (NIH). The fiscal year 2015 budget of $372,851,000 includes an increase of $5,628,000 over the comparable fiscal year 2014 level of $367,223,000.

The National Library of Medicine, the world's largest biomedical library, builds and provides electronic information resources used billions of times each year by millions of scientists, health professionals and members of the public. Many health information searches that are initiated on the Internet actually retrieve information from an NLM Web site. NLM is crucial in the dissemination of biomedical research results—DNA sequences, clinical trials data, toxicology and environmental health data, research publications, and consumer health information to scientists, health professionals, and the public. A leader in biomedical informatics and information technology, NLM also supports and conducts research, development, and training in biomedical informatics, data science, and health information technology; and coordinates the 6,100-member National Network of Libraries of Medicine that promotes and provides access to health information in communities across the United States.

NLM's programs and services directly support NIH's key initiatives in basic research, precision medicine, research training, as well as in data science and Big Data. NLM's National Center for Biotechnology Information (NCBI) is a focal point for "Big Data" in biomedicine and a leader in organizing and providing rapid access to massive amounts of genetic sequence data generated from evolving high-through-

put sequencing technologies. NCBI serves more than 30 terabytes of biomedical data to more than 3.3 million users daily. Some of the largest datasets, such as those from NIH's 1000 Genomes Project, are also available in the Amazon cloud. This allows faster access and analysis by researchers who may be otherwise hampered by insufficient bandwidth or computing power. Additionally, the Library organizes and provides access to the published medical literature; assembles data about small molecules to support research and therapeutic discovery; provides the world's largest clinical trials registry and results database; and is the definitive source of published evidence for healthcare decisions. NLM's PubMed Central (PMC) provides essential infrastructure for the NIH Public Access Policy, making published NIH-funded research freely and permanently available to the public. NLM/NCBI databases are cited in laws and Congressional legislation (e.g., Public Law 110–161,Consolidated Appropriations Act and HR 4186, the Frontiers in Innovation, Research, Science, and Technology) as a model for facilitating public access to federally funded data and publications.

Research supported or conducted by NLM underpins today's electronic health record systems. The Library has been the principal funder of university-based informatics research training for 40 years, supporting the development of today's leaders in informatics research and health information technology. NLM's databases and its partnership with the Nation's health sciences libraries deliver research results wherever they can fuel discovery and support health decisionmaking.

BIOMEDICAL AND HEALTH INFORMATION SERVICES

NLM's PubMed/MEDLINE database is the world's gateway to research results published in the biomedical literature. It links to full-text articles in PubMed Central, including those deposited under the NIH Public Access Policy, and on publishers' Web sites, as well as connecting to vast collections of scientific data. PubMed contains more than 23 million references to articles in the biomedical and life sciences journals providing high quality information to about 2.3 million users per day. NLM is a primary source for results of patient-centered outcomes research, providing access to evidence on best practices to improve patient safety and healthcare quality. NLM is also a hub for the international exchange and use of data utilized in molecular biology, genomics, and clinical and translational research. Many NCBI databases, including dbGaP, the Genetic Testing Registry (GTR), and ClinVar are fundamental to the identification of important associations between genes and disease, and to the translation of new knowledge into better diagnoses and treatments.

NLM's Lister Hill National Center for Biomedical Communications operates ClinicalTrials.gov, the world's most comprehensive clinical trials database. It contains registration data for more than 160,000 clinical studies with sites in 185 countries and summary results for more than 11,000 trials, including many results that are not available elsewhere.

STANDARDS FOR ELECTRONIC HEALTH RECORDS

For 40 years, NLM has supported seminal research on electronic patient records, clinical decision support, and health information exchange, including concepts and methods now reflected in electronic health record (EHR) products and personal health record tools. EHRs with advanced decision-support capabilities and connections to relevant health information are essential to improving healthcare and helping Americans manage their own health. As the Department of Health and Human Services (HHS) coordinating body for clinical terminology standards, NLM works closely with the Office of the National Coordinator for Health Information Technology and the Centers for Medicare and Medicaid Services to facilitate adoption and "meaningful use" of EHRs. NLM supports, develops, and distributes key terminology standards now required for U.S. health information exchange. To help EHR developers implement standard terminologies, NLM produces related software tools, frequently used subsets, and mappings to administrative code sets, and provides the authoritative versions of terminology value sets for required clinical quality measures. NLM's MedlinePlus Connect also supports meaningful use by providing a way for EHR products to link patients to high quality health information relevant to a specific health conditions, medications, and tests, directly from their EHRs.

HEALTH INFORMATION FOR THE PUBLIC

The NLM has a wide range of outreach programs to enhance awareness of NLM's diverse information services among biomedical researchers, health professionals, librarians, patients, and the public. To improve access to high quality health information, NLM works with the 6,100 institutions of the National Network of Libraries of Medicine, a network of academic health sciences libraries, hospital libraries, pub-

lic libraries, and community-based organizations and has formal partnerships with tribal colleges and other minority serving institutions. In fiscal year 2013, dozens of community-based projects were funded across the country to enhance awareness and access to health information, including in disaster and emergency situations, and to address health literacy issues.

The Library's MedlinePlus Web site provides integrated access to high quality consumer health information produced by all NIH components and HHS agencies, other Federal departments, and authoritative private organizations. It serves as a gateway to specialized NLM information sources for consumers, such as the Genetic Home Reference and the Household Products Database. Available in English and Spanish, with selected information in 40 other languages, MedlinePlus averages well over 750,000 visits per day. Mobile MedlinePlus, also in both English and Spanish, reaches the large and rapidly growing mobile Internet audience.

The NIH MedlinePlus print and online magazine, in English and Spanish, is an outreach effort made possible with support from many parts of NIH and the Friends of the NLM. Distributed free to the public via physician offices, community health centers, libraries and other locations, the print magazine reaches a readership of up to 5 million nationwide and the online version reaches millions more. Each issue focuses on the latest research results, clinical trials and guidelines from the 27 NIH Institutes and Centers.

The Library diversifies access to all its information resources, through mobile devices and "apps." NLM continues to be a leading player in social media amongst HHS agencies with active Facebook, Twitter, and You Tube accounts, including the very popular @medlineplus Twitter feed and a Spanish-language counterpart, several online newsletters, and its National Network of Libraries of Medicine, which covers the United States and hosts eight Facebook pages, 10 Twitter feeds and 12 blogs. NLM is consistently ranked among the most liked, most followed, and most mentioned organizations amongst small government agencies with social media accounts.

In conclusion, the Library is a trustworthy source of health information for the public and vital to the practice of 21st century medicine and the progress of science. NLM's information services and research programs serve the Nation and the world by supporting scientific discovery, clinical research, education, healthcare delivery, public health response, and the empowerment of people to improve personal health. The Library is committed to the innovative use of computing and communications to enhance public access to the results of biomedical research.

PREPARED STATEMENT OF JON R. LORSCH, PH.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget for the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH). The fiscal year 2015 budget of $2,368,877,000 includes an increase of $6,983,000 above the comparable fiscal year 2014 level of $2,361,894,000. NIGMS considers its public funds a precious resource and focuses on efficiency and effectiveness in making investments in research and training. The Institute spends 97 percent of its budget outside of the NIH, funding biomedical research and training at universities and other institutions across the country—where creative minds are at work every day producing new knowledge about health and disease.

Scientific discovery is the engine for advances in medicine, as research results lead to new treatments and refine current standards of care. Biomedical research relies on attracting and retaining a creative and well-trained workforce. NIGMS remains committed to enabling researchers throughout the United States to answer important scientific questions in fields such as cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, biomedical technology, bioinformatics, computational biology, selected aspects of the behavioral sciences and specific cross-cutting clinical areas that affect multiple organ systems. To assure the vitality and continued productivity of the research enterprise, NIGMS also provides leadership in training the next generation of scientists as well as in developing and increasing the diversity of the scientific workforce.

BACK TO BASICS

The high value of investigator-initiated research has stood the test of time. This approach, in which scientists decide what questions are important to study, ultimately leads to major advances in medicine and technology. Examples include:

—Studies of virus-resistant bacteria led to the discovery of restriction enzymes, which act like highly specific scissors for cutting DNA. This discovery launched

the multi-billion-dollar biotechnology industry, starting with the laboratory-based production of life-saving medicines like insulin and now extending even beyond biomedicine into agriculture and biofuels.

—Seemingly esoteric studies of how electric fields affect DNA replication in bacteria lead directly to the discovery of the anti-cancer drug cisplatin, which has saved thousands of human lives.

—Studies of enzymes that copy DNA and RNA and that cut proteins enabled the development of drugs to treat HIV infection.

To ensure a continued pipeline of fundamental scientific advances that will lead to future medical and technological breakthroughs, NIGMS is rebalancing its portfolio to renew and reinvigorate its support for question-driven, investigator-initiated research. This rebalancing has received strong support from stakeholder organizations, including the Federation of American Societies for Experimental Biology, an umbrella group representing 26 scientific societies and over 115, 000 researchers.

PLANNING CAREFULLY FOR THE FUTURE

NIGMS has begun a new strategic planning process that is focusing on enhancing the efficacy, efficiency, and adaptability of the Institute's internal processes and the mechanisms through which we support biomedical research. In particular, we are exploring the development of new grant mechanisms that would increase stability and flexibility for researchers and maximize the scientific return on taxpayers' investment. These mechanisms will focus on the efficient use of funds, encouraging scientists to undertake ambitious and creative projects that may be the breakthroughs of tomorrow.

NIGMS is also developing new strategies to strengthen and maintain the pipeline of talented, creative, diverse and highly skilled young investigators. This segment of the biomedical workforce is essential for the future of scientific research in the United States, which is in turn essential for the future health and economic competitiveness of our Nation. Specific strategies we are considering to address the challenges facing young investigators include outcomes-based enhancements of our training programs and efforts to improve the competitiveness of young investigators in obtaining and keeping research grants.

SUPPORTING A DIVERSITY OF IDEAS

NIGMS is proud to be the home of the IDeA program, which ensures that cutting-edge research is conducted in every region of the country. This strategy is critical to the strength of our biomedical research enterprise, as it meets the need to involve the most diverse set of minds, experiences and approaches for solving difficult health-related problems. Last year, NIGMS funded or co-funded 58 competing grants to IDeA researchers, this included 25 competing Centers of Biomedical Research Excellence awards. Particularly exciting research developments funded by the IDeA program include the demonstration by Kentucky researchers that electrical stimulation of the spinal cord can restore some motor function in individuals with paraplegia; a study by scientists in South Carolina showing that nanoparticles coated with antioxidant proteins can protect against stroke-related damage; and a neonatal telemedicine center in Arkansas that has contributed to a significant decrease in statewide infant mortality.

As requested by both the House and Senate and required by the Consolidated Appropriations Act of 2014, NIH has submitted a response to the National Academies' Report on EPSCoR and related programs. As part of the NIGMS strategic planning process, we are developing plans for enhancing access to resources for moving discoveries and innovative ideas from laboratories in IDeA states into commercial products. In particular, we are exploring support for regional biotechnology incubators that would give faculty in IDeA states access to laboratory space, equipment, expertise, and advice required to make their work competitive for SBIR/STTR and venture capital funding.

ADVANCING HEALTH THROUGH DISCOVERY

This past year, NIGMS-funded scientists broke new ground in a range of areas relevant to health, including chemistry, microbe-host interactions, computer modeling, and metabolism. Selected examples include:

—A Tennessee researcher developed a chemical method to shave the cost of manufacturing expensive drugs, including those used to treat HIV/AIDS. The method is also environmentally friendly in that it employs natural molecules called enzymes instead of synthetic chemicals that are often hazardous.

—A scientist from Vermont created the first-ever interaction map of human proteins that attach to proteins from arenavirus and hantavirus, providing poten-

tial new targets for therapies to treat the often deadly illnesses caused by these classes of viruses.

—A Pennsylvania researcher found compounds that block a recently discovered pathway for preventing production of damaged proteins. These chemicals have antibiotic activity, suggesting they might eventually be developed into a new class of antibacterial drugs.

—A scientist from California learned from mouse studies that a high-fat diet influences the internal body clock controlling liver metabolism. The team also discovered that the effect was reversible by returning to a balanced, low-fat diet.

These discoveries are a small subset of the productivity of the nearly 4,000 scientists NIGMS supports throughout the United States. Our public investment to fuel their curiosity-driven exploration of biomedicine is growing knowledge, and local economies, as well as improving the health of all Americans.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee may have.

PREPARED STATEMENT OF YVONNE T. MADDOX, PH.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget for the National Institute on Minority Health and Health Disparities (NIMHD) of the National Institutes of Health (NIH). The fiscal year 2015 budget of $267,953,000 is the same as the fiscal year 2014 enacted level of $267,953,000.

INTRODUCTION

As the primary Federal agency for leading, coordinating and facilitating research to improve minority health and eliminate health disparities, NIMHD impacts the lives of millions of Americans burdened by disparities in health status and healthcare delivery, including racial and ethnic minority groups as well as rural and low-income populations. A population is a health disparity population if it is determined that there is a significant disparity in the overall rate of disease incidence, prevalence, morbidity, mortality, or survival rates in the population as compared to the health status of the general population. The elimination of health disparities requires a multidisciplinary approach, with collaboration, coordination, and integration across NIH Institutes and Centers (ICs), other Federal agencies and private-sector organizations to fully understand and solve the underlying biological and non-biological causes of health disparities.

FUNDAMENTALS OF HEALTH DISPARITIES

In order to understand the social, behavioral, biological, and environmental factors influencing health disparities, NIMHD is studying the fundamental causes of diseases and conditions that disproportionately affect individuals from health disparity backgrounds. For example, one project studies the higher incidence and mortality of breast cancer in African American women through research that examines the role genetic differences in the tumor suppressor protein, p53, plays in the disparity. Researchers hypothesize that some racial/ethnic groups have disproportionate p53 variants that may contribute to breast cancer health disparities in the age of onset, incidence, and lack of pregnancy protection in African American women. Another study takes knowledge about causal pathways learned at the bench and extends the findings to social, behavioral, health services and/or policy approaches to test ways to improve minority health and eliminate health disparities. This project examined unconscious stereotyping of Hispanic patients among medical and nursing students. The study found that students endorsed stereotypes that Hispanic patients would be non-compliant or likely to engage in high-risk health behaviors, even if the students reported trying consciously to avoid biased thinking. This unconscious bias of medical providers can be one factor in the disparity in healthcare delivery faced by minority patients.

COLLABORATIVE RESEARCH FRAMEWORK

Comprehensively addressing health disparities requires a transdisciplinary framework that fosters an integrated approach involving biology, behavioral and social sciences, environmental science, public health, healthcare delivery, economics, public policy, and many other disciplines. It also requires strong collaborations between researchers and community organizations, service providers and systems, government agencies, and other stakeholders to ensure that contextually appropriate and relevant research is conducted, and that findings can translate into sustainable individual, community, and systems level changes that improve the health of the U.S.

population. The NIMHD supports two programs that focus on transdisciplinary and translational research: the Centers of Excellence (COE) and the Transdisciplinary Collaborative Centers for Health Disparities Research (TCC). The COEs, which were established as partnerships between academic institutions and community organizations, have been in place for over a decade and have reached more than 102 sites, across 31 States, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. The COEs are addressing health disparities research along the translational spectrum from basic science to clinical research, with information dissemination a required component.

The TCC Program, established in fiscal year 2012, supports research, implementation, and dissemination of activities that transcend customary discipline-specific approaches conducted at the local level. Transdisciplinary research collaboration at the regional level provides opportunities for academic institutions, community-based organizations, and other partners to conduct targeted research to respond to specific population-based, environmental, sociocultural, and political factors that influence health within a particular region.

The Collaborative Research Center for American Indian Health is bringing together tribal communities and health researchers from a variety of disciplines to work together to address the significant health disparities experienced by American Indians in South Dakota, North Dakota and Minnesota, particularly the social determinants of health and its application to programming public health interventions. The National Transdisciplinary Collaborative Center for African American Men's Health is addressing unintentional and violence-related injuries as well as chronic diseases that affect African American men across the life course, as part of a national initiative.

COMMUNITY ENGAGEMENT

Active community involvement in biomedical and behavioral research is essential to improving the health of the public. The NIMHD Community-Based Participatory Research (CBPR) Initiative supports the development, implementation, and evaluation of intervention research that utilizes the principles of community engagement as partners in the full spectrum of research. A number of CBPR planning phase and dissemination phase projects are under way. The Partnerships to Improve Lifestyle Interventions and Partners in Care programs tested the effectiveness of a culturally adapted diabetes self-management intervention among Native Hawaiians and Pacific Islanders. The study found improvements in weight loss, physical capacity, and diabetes self-management.

Another CBPR project focused on a culturally appropriate, church-based Hepatitis B screening and vaccination intervention program for Korean Americans which found increased screening and immunization rates in the intervention group compared with the control group. Academic-community partnerships were essential in balancing science and community needs in the design and conduct of the needs assessment, pilot and full-scale clinical trial.

RESEARCH TRAINING AND INFRASTRUCTURE

In order to advance the science and speed translation of discoveries into better health outcomes for all Americans, it is critical to expand and diversify the Nation's workforce of well-trained scientists who are dedicated to improving minority health and eliminating health disparities. A diverse biomedical workforce will improve the quality of the educational and training environment, balance and broaden the perspective in setting research priorities, improve the ability to recruit subjects from diverse backgrounds into clinical research protocols, and improve the Nation's capacity to address and eliminate health disparities. NIMHD-supported programs to train researchers to conduct minority health and health disparities research are focusing on providing educational, mentoring, and/or career development programs for individuals from health disparity populations that are underrepresented in the biomedical, clinical, behavioral, and social sciences. NIMHD continues to support research training and infrastructure through its Research Endowment Program, Building Research Infrastructure and Capacity Program, and Research Centers in Minority Institutions Program.

CONCLUSION

NIMHD has a unique and critical role at the NIH as the focal point for conducting and coordinating research on minority health and health disparities, raising national awareness about the prevalence and impact of health disparities, and the dissemination of effective individual, community, and population-level interventions to reduce and ultimately eliminate health disparities. NIMHD is looking forward to

identifying new opportunities to accelerate the pace of research and to advance its mission through strengthening partnerships and enhancing its role in the community.

PREPARED STATEMENT OF RODERIC I. PETTIGREW, PH.D., M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Biomedical Imaging and Bioengineering (NIBIB) of the National Institutes of Health (NIH). The fiscal year 2015 NIBIB budget request of $328,532,000 is $2,173,000 more than the fiscal year 2014 enacted level of $326,359,000.

NIBIB is dedicated to improving human health through the integration of the physical and biological sciences. NIBIB's mission spans the entire health spectrum and is not limited to a single disease, group of illnesses, or population. Working with doctors from every field of medicine and bringing together teams of scientists and engineers from many different backgrounds, NIBIB aims to develop innovative approaches to healthcare. Our research focus is to improve the understanding, detection, treatment and ultimately, the prevention of disease.

INNOVATION IN TREATING SPINAL CORD INJURY: NEW HOPE FOR THOSE WITH PARALYSIS

Building on a long history of research on restoring function in spinal cord injury, researchers have discovered a fundamentally new intervention that led to voluntary movement in individuals with complete paralysis. This outcome, initially seen in a single individual, has now been reported in three successive patients, all of whom had been paralyzed for more than 2 years. This achievement is a significant milestone in spinal cord injury research. In the approach, electrical stimulation is applied to the surface of the spinal cord through a surgically implanted device that is normally used for the suppression of back pain. After just a week of stimulation, on average, the patients were able to voluntarily move their legs and flex their feet and toes when the stimulator was turned on. With continued daily stimulation and extensive physical training, the patients saw improvements in their movements and could initiate them with decreased stimulation. With their stimulators turned on, the patients are now able to stand for about an hour. Restored function was accompanied by increased muscle mass. In addition, these individuals have regained bladder and bowel function and experienced improvements in autonomic responses such as sweating and return of sexual function in some cases.

IMMUNOENGINEERING TO MODIFISCAL YEAR IMMUNE SYSTEM RESPONSES

The immune system is the body's defense against an array of infectious agents. However, the immune system can also trigger many diseases such as diabetes, rheumatoid arthritis, lupus or multiple sclerosis; this occurs when immune cells are directed against an individual's own cells and is referred to as autoimmunity. As our understanding of the immune system increases, we are approaching a point where the immune response can be engineered to enhance or reduce specific responses. Two recent examples highlight this "immunoengineering" approach. In the first case, the problem being addressed is improving targeted delivery of chemotherapeutic drugs to tumors. Nanoparticles can be used to ferry chemotherapy directly to tumors, minimizing exposure of these toxic medications to healthy tissues in the body. Researchers have found a way to ferry nanoparticles carrying chemotherapy drugs past cells of the immune system, which would normally engulf the particles, preventing them from reaching their target. The technique takes advantage of the fact that all cells in the human body display a protein on their membranes that functions as a specific "passport" in instructing immune cells not to attack them. By attaching a small piece of this protein to nanoparticles, scientists were able to get immune cells in mice to recognize the particles as "self" rather than foreign particles, and thereby not attack them. The nanoparticles also have other labels that can concentrate the drugs in the tumors, so higher doses of chemotherapy are delivered to the tumor.

In a second example, researchers have developed a strategy to modulate the immune system to halt the progress of a disease model of multiple sclerosis in mice. In multiple sclerosis, the immune system attacks the myelin sheaths that surround nerve cells. To stop this attack, engineered nanoparticles are coated with myelin antigens, and these nanoparticles are presented to another set of cells in the immune system that re-identifies myelin as 'self' rather than 'foreign'. The result is that the immune system stops attacking myelin as a foreign body, and the disease progression is halted. This approach begins to take advantage of the complex control

of immune response which contains multiple positive and negative feedback loops in order to selectively turn off one specific inflammatory response. It holds promise for treating multiple sclerosis and other autoimmune diseases that previously have escaped effective therapies.

CANCER DETECTION FROM A ROUTINE BLOOD SAMPLE

Most cancers spread by way of the circulatory system. As a result, there are cancer cells present in blood samples. The number of cells, however, is so low that they have been difficult or impossible to find. The problem is to find and isolate the few cancer cells from the billions of other cells that are present in the blood. Researchers over the past several years have developed new techniques to find these cells, but those techniques have generally been destructive to the cancer cells. Now, with a new sorting technology, researchers have demonstrated the ability to sort the cancer cells and, of equal importance, to collect them for further analysis. After collection, the circulating tumor cells can be subjected to the full array of analysis techniques available to normal tissue biopsies of a tumor. This technology also permits sorting, using a variety of markers that allow, for example, the identification of triple negative breast cancer cells. Successful isolation has been demonstrated in several other cancers including lung, prostate, pancreas, breast, and melanoma. This new tool has the potential to improve both the early diagnosis and effective treatment of cancer.

AN IMPLANTABLE ARTIFICIAL KIDNEY HOLDS PROMISE FOR PATIENTS ON DIALYSIS

Expenditures in the United States for end stage renal disease exceed $40 billion annually. Treatment of end stage renal disease includes renal transplant and thriceweekly, in-center hemodialysis. Renal transplant is limited to a small fraction of potential recipients by a shortage of donor organs. As a result, more than 400,000 Americans are on dialysis, which is expensive, inconvenient, and over time associated with significant morbidity and mortality. Researchers are developing an implantable bioartificial kidney called the Implantable Renal Assist Device (iRAD), in which a patient's blood will be filtered through an artificial kidney consisting of silicon nanopore membranes and a bioreactor of cells to mimic the functions of a healthy kidney. Such a device could offer numerous advantages for patients including: freedom of mobility, decreased infection risk due to a permanent vascular connection, and continuous treatment, which avoids the build-up of toxins that occurs between in-center hemodialysis visits. In addition, incorporation of the patient's own cells could provide normal renal metabolic function that would be more physiologic than dialysis and not require anti-rejection drugs used for transplant. This combined filtration and metabolic treatment has been shown to work using a room-sized external model. Multi-day animal model testing to demonstrate hemofilter biocompatiblity has been conducted. Although human studies have not been initiated with the iRAD, these researchers are working with the Food and Drug Administration (FDA) on an initiative that facilitates new ways for FDA staff and innovators to jointly bring breakthrough medical device technologies to patients faster and more efficiently.

SMART HOMES FOR HEALTHY INDEPENDENT LIVING AT ALL AGES

The population is aging and, increasingly, medical treatment involves the management of chronic and/or degenerative diseases. Management of such conditions requires monitoring and early intervention to prevent more severe complications. The rapid development and ever expanding capabilities of smart phones, advanced sensors, point-of-care diagnostics, and integrated Internet connectivity provides a framework on which new healthcare models can be developed to provide this monitoring and intervention. Investigators are testing real-time home observation of high-risk patients for early signs of illness, using a built-in camera, computer tablet and a smart phone for simultaneous monitoring of daily activities by family members and health professionals. This includes analysis of daily habits, mobility patterns, and gait rate and rhythm as indicators of change in health status. Developing automated technologies to help identify early indicators of changes in health status will extend the amount of time individuals can live independently in their own homes.

PREPARED STATEMENT OF GRIFFIN P. RODGERS, M.D., M.A.C.P.

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2015 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH).

The fiscal year 2015 budget includes $1,743,336,000, which is $1,462,000 above the comparable fiscal year 2014 appropriation of $1,741,874,000. Complementing these funds is an additional $150,000,000 authorized in fiscal year 2015 from the Special Statutory Funding Program for Type 1 Diabetes Research. NIDDK supports research on a wide range of common, chronic, costly, and consequential diseases and health problems that affect millions of Americans. These include diabetes and other endocrine and metabolic diseases; digestive and liver diseases; kidney and urologic diseases; blood diseases; obesity; and nutrition disorders.

TODAY'S BASIC SCIENCE FOR TOMORROW'S BREAKTHROUGHS

NIDDK-supported basic research is achieving remarkable progress and building the foundation for previously unimaginable strategies to improve health and quality of life. For example, recent research has better defined human brown adipose (fat) tissue in the neck, and has further elucidated the role of a family of proteins as molecular signals regulating brown fat physiology—findings that could help inform new approaches for altering metabolism to clinical advantage. The microorganisms that inhabit the gastrointestinal tract are important factors in maintaining or tipping the balance between health and disease. A recent study of young twin pairs in Malawi revealed that gut microbes may play an important role in causing severe malnutrition in children that persists in spite of nutritional interventions. Gaining new insight into gastric bypass surgery, scientists studying a mouse model found that restructuring of the digestive tract leads to weight loss and metabolic benefits in part by altering the communities of bacteria that normally live in the intestines. Another study has shown that deletion of the protein olfactomedin-4 in white blood cells improves their ability to eradicate infections with the harmful bacteria Staphylococcus aureus in an animal model of the immune disorder chronic granulomatous disease. Scientists supported by our Institute have used a series of genetically engineered mice to identify the contribution of different kidney cell subtypes to the process of fibrosis that follows kidney injury, confirming myofibroblasts' contribution to fibrosis and tracking their developmental origins—results that could inform future treatment strategies. Scientists have discovered a link between two proteins known to contribute to the most common form of polycystic kidney disease and a cell-surface structure in a subset of kidney cells in mice. NIDDK-supported researchers conducted a study in mice showing that chemotherapy damages nerves that regulate bone marrow niches responsible for making new blood cells; future research in humans could explore ways to reduce nerve damage and improve blood cell regeneration after chemotherapy. A new study has shown that it may one day be possible to treat people with cystic fibrosis (CF) using a combination of medicines that work cooperatively to stabilize an aberrant form of CFTR, the protein that is defective in CF.

NIDDK will continue support for basic research across the Institute's mission, to gain further insights into health and disease and propel new ideas for interventions. Areas of emerging opportunity include research on generating or repairing nephrons that can function within the kidney; diet-host microbiome interactions in autoimmune and metabolic diseases; and a collaborative research network on disease modeling and tissue repair and regeneration.

CLINICAL SCIENCE AND PRECISION MEDICINE

Through innovative design and rigorous testing of interventions—whether in the operating room, doctor's office, or home or community settings—NIDDK-supported researchers are improving lives with new approaches to prevent, treat, and reverse diseases and disorders. For example, researchers studying type 1 diabetes have used smartphone technology to move a step closer toward developing an artificial, bionic, pancreas. Scientists reported data on insulin resistance and secretion that suggest early and rapid deterioration of pancreatic beta cell function in youth with type 2 diabetes, underscoring the need to intervene early and aggressively. Researchers have found that patients with irritable bowel syndrome show an improvement in symptoms following a short course of group therapy involving psychological and educational approaches. Recent research has shown that in dialysis patients with diabetes, measuring another set of modified blood proteins may better predict the risk of death and cardiovascular disease than the current standard test to assess blood glucose control.

The NIDDK supports research aimed at tailoring treatments for disease to the individual characteristics of each patient. For example, a detailed genetic study has now identified rare mutations of the SLC30A8 gene that sharply reduce risk for type 2 diabetes in several different racial/ethnic populations, suggesting that inhibitors of the Slc30A8 protein may one day be therapeutically valuable. New research

has greatly expanded knowledge of the specific genetic mutations capable of causing CF, leading to much more comprehensive CF genetic testing. A recently discovered set of mutations in the DGKE gene may be behind some cases of the serious blood disorder hemolytic uremic syndrome. Scientists participating in NIDDK's Childhood Liver Disease Research and Education Network have utilized patient samples and an animal model to identify a genetic deletion in the GPC1 gene that may play a role in the development of biliary atresia. NIDDK researchers have created and confirmed the accuracy of a mathematical model that predicts how weight and body fat in children respond to adjustment in diet and physical activity.

NURTURING TALENT AND INNOVATION

NIDDK will continue programs to train and support researchers at all stages of their careers, and to ensure that we benefit from the best scientific minds. One major objective of the Network of Minority Health Research Investigators is to encourage and facilitate participation of members of underrepresented population groups and others interested in minority health in the conduct of biomedical research. In addition, several NIDDK-sponsored programs provide opportunities for minority students to obtain research experience. The NIDDK's Short-Term Education Program for Underrepresented Persons, or STEP-UP, provides research education grants to seven institutions to coordinate high school and undergraduate STEP-UP programs that enable students to gain summer research experience and training.

INTEGRATING SCIENCE-BASED INFORMATION INTO PRACTICE

NIDDK also will continue to support education, outreach, and awareness programs. Research clearly shows that communications alone about the seriousness of diabetes will not reverse the diabetes epidemic. The NIDDK is committed to focusing more efforts to promote the theme of moving from awareness to action, by providing behavior change tools and other resources to help people with diabetes and those at risk make and sustain lifestyle changes. For example, the NIDDK-CDC National Diabetes Education Program has developed the Diabetes HealthSense Web site, an online library of tools and resources developed by partners from around the country to address a wide array of psychosocial and lifestyle challenges. The NIDDK's National Kidney Disease Education Program (NKDEP) works to identify people with chronic kidney disease (CKD) and promote the implementation of evidence-based interventions, focusing on populations at highest risk for CKD and the providers who serve them. In addition, through collaborative community partnerships with organizations such as the Chi Eta Phi Nursing Sorority and the American Diabetes Association, NKDEP brings NIH science-based information to the grassroots.

In closing, NIDDK's future research investments will be guided by five principles: maintain a vigorous investigator-initiated research portfolio; support pivotal clinical studies and trials; preserve a stable pool of new investigators; foster research training and mentoring; and disseminate science-based knowledge through education and outreach programs.

PREPARED STATEMENT OF PAUL A. SIEVING, M.D., PH.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Eye Institute (NEI) of the National Institutes of Health (NIH). The fiscal year 2015 budget proposal is $675,168,000, which is $0.9 million more than the fiscal year 2014 enacted level of $674,249,000. As the director of the NEI, it is my privilege to report on the many research opportunities that exist to reduce the burden of eye disease.

NEI AUDACIOUS GOAL INITIATIVE

Vision research is often on the cutting edge of biomedical research, from the first successful gene therapy clinical trials that restored some visual function in patients with an inherited form of blindness, to clinical trials for macular degeneration using tissue derived from embryonic stem cells, to a retinal electrical prosthesis, approved this past year by the FDA, after years of development by Second Site, a small business that received research support from both NEI and the Department of Energy. NEI is now starting a new chapter in its ambitious research agenda. I have launched a new initiative—The NEI Audacious Goal Initiative in Vision Research and Blindness Rehabilitation—to identify a groundbreaking long-term research goal that will markedly improve prevention and treatment of common eye diseases.

We started this effort over a year ago by soliciting audacious ideas from scientists, stakeholders, patients, clinicians, and the public through a Challenge Competition. After a thorough scientific review of more than 500 submissions, we chose 10 winning entries, which were presented and intensively discussed at the NEI Audacious Goals Development Meeting last year. In May, I announced that the NEI Audacious Goal will be to Regenerate Neurons and Neural Connections in the Eye and Visual System. To kick start this initiative, we will soon release funding opportunities focusing on different components of this goal. Implementation of work toward the goal will include oversight, guidance, and direction from non-governmental consultant experts.

This goal will focus on two types of retinal neuronal cells that underpin many of the leading causes of visual impairment. One such target is photoreceptor cells, the specialized neurons in the retina that detect light and initiate the neural response. Blindness in some diseases, such as retinitis pigmentosa, is a direct result of photoreceptor cell death, whereas in other diseases such as diabetic retinopathy or macular degeneration, damage elsewhere in the retina indirectly causes photoreceptor cells to die.

Retinal ganglion cells (RGCs) are the second cell type targeted in this program. These neurons reside in the retina but send long projections (axons in the optic nerve) that connect to the brain. When RGCs degenerate and die in diseases such as glaucoma and multiple sclerosis, vision signals from the eye can't get to the brain. Two of the primary scientific challenges of this initiative include protecting newly regenerated cells from dying, and inducing them to form appropriate neural connections in the brain. Success in achieving this goal will not just revolutionize how we approach diseases in vision, but all of neuroscience.

NEI is also a key contributor and participant in the President's BRAIN initiative, which seeks to decode the brain, just as the Human Genome Initiative decoded DNA. While NEI's Audacious Goal is independent from the BRAIN initiative, the eye is the gateway to the brain—it is the most accessible part of the central nervous system. There is good opportunity for synergy between these exciting initiatives.

NEW AREAS OF EMPHASIS

In the process of identifying our Audacious Goal, we also identified two high-priority, complementary areas of emphasis, for which we have released two funding opportunities and are currently reviewing grant applications: Molecular Therapy for Eye Disease; and the Intersection of Aging and Biological Mechanisms of Eye Disease. With recent advances in genomics, we now have a good understanding of genes and molecules that are altered in many diseases. The National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE), is a critical resource created by NEI for identifying the mutated genes in patients with inherited eye disorders and giving researchers access to DNA samples (over 4,000 collected since 2006), clinical information, and patients looking to participate in research studies. But the current tools at our disposal to treat genetic diseases are limited. Building on our recent successes in gene therapy, the exciting potential of designing personalized therapies to correct mutant genes lies in the research ahead of us over the next decade.

Many eye diseases are associated with aging: from cataracts and presbyopia, which are common in all adults as they age, to some of the leading vision impairment diseases, age-related macular degeneration (AMD) and glaucoma. Understanding what aspects of the aging process contribute to eye disease has the potential to delay the onset of vision loss or even avert the disease.

NEI REGENERATIVE MEDICINE PROGRAM

Also contributing to the Audacious Goal Initiative are researchers at NEI, working with the NIH Center for Regenerative Medicine to create retinal tissues from induced pluripotent stem (iPS) cells for several basic and translational research applications. iPS cells can be generated from any adult cell, and then converted into virtually any other type of cells. A major thrust of this program is to derive iPS cells from patients with retinal diseases. Then, the iPS cells are differentiated to form retinal pigment epithelial (RPE) cells or photoreceptors and studied to identify disease-causing molecular pathways. Diseases of interest currently include AMD, Best disease, late-onset retinal degeneration, Stargardt's disease, and retinitis pigmentosa. This program is exploiting these techniques to develop high-throughput drug screens to identify potential therapeutic compounds for treating retinal degenerative diseases.

Another potentially powerful application of iPS cell technology is to generate iPS cells from normal tissue and then differentiate those cells into monolayer sheets of RPE for tissue transplants. NEI intramural investigators are engineering a bio-de-

gradable scaffold in order to grow the RPE tissue and transfer it to patients with RPE-associated retinal degenerative diseases. In fiscal year 2015, the stem cell program will also use stem cell technologies to evaluate synaptic connections in 3–D retinas derived from iPS cells.

As I reflect on the remarkable progress the vision community has made in these past few years, I can hardly anticipate the exciting opportunities that lay ahead.

PREPARED STATEMENT OF MARTHA SOMERMAN D.D.S., PH.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Dental and Craniofacial Research (NIDCR) of the National Institutes of Health (NIH). The fiscal year 2015 NIDCR budget of $397,131,000 includes an increase of $29,000 over the enacted fiscal year 2014 level of $397,102,000.

In keeping with its mission to improve the Nation's oral health, the breadth of NIDCR's research touches the lives of nearly all Americans. Our research spans multiple disciplines, scientific approaches, and research directions, all focused on the goal of improving people's lives. Today, I will highlight selected areas of particular promise in our efforts to understand the development of tissues of the face and head, conquer oral infectious diseases through better understanding of the body's own defenses, help people facing chronic orofacial pain conditions, and develop new approaches to improve oral cancer survival.

DEVELOPMENT AND REGENERATION

The human face is among the body's most distinctive structures. NIDCR is the leading supporter of research on the development of the human face and skull, collectively known as the craniofacial region. By defining the complex web of environmental and genetic instructions that drive craniofacial development, the hope is that scientists one day will learn to repair damaged or malformed facial structures such as cleft lip and palate by harnessing the body's ability to heal itself.

Five years ago, NIDCR began assembling information on the genetic code that instructs facial development with the launch of its FaceBase Consortium. Through this endeavor, scientists have assembled nearly 500 publicly available datasets involving the biological instructions for the middle region of the human face, which includes the nose, upper lip, and palate, or roof of the mouth. FaceBase begins a second phase this year, as it expands its focus to include studies on additional regions of the face. This new phase will add to our knowledge about the genetics that underlie craniosynostosis, a birth skull defect that may result in severe and permanent problems if not corrected.

NIDCR is also translating knowledge about craniofacial development into tools to re-grow bone and cartilage damaged by disease or injury. Ongoing studies are using the power of stem cells to regenerate tissues, improve wound healing, and help control inflammatory-associated diseases of the mouth. Related research uses specially designed stable small molecules modified from naturally occurring molecules called resolvins that control inflammation in a wide range of conditions to target oral inflammatory diseases such as periodontitis. We envision a future where natural tool kits are used to regenerate and repair damaged teeth, diseased gums, and broken or defective bones by utilizing stem cells and adapting natural molecules and processes.

ORAL INFECTIONS, IMMUNITY AND THE MICROBIOME

The NIH's human microbiome project has reinforced that no man is an island. Although human beings coexist with a plethora of microorganisms, microbial cells outnumber human cells by 10 to 1, living on surfaces of our body in sticky layers of polymicrobial communities called biofilms. Under normal circumstances, these microbial guests coexist with us and even contribute to sustaining human health. But, if conditions in some part of the body are altered, the balance is disrupted, and the disease-causing organisms that live on our gums and teeth can overwhelm our natural immune defense systems causing oral infectious diseases such as tooth decay and periodontal diseases. NIDCR-supported scientists are beginning to assemble the precise molecular details of how select oral pathogens destabilize the immune system to cause oral diseases. For example, individuals with leukocyte adhesion deficiency (a rare genetic disorder affecting the body's immune system) suffer from frequent bacterial infections, including severe periodontitis. New research has demonstrated that blocking certain molecules that are part of the individual's own immune system can reverse this inflammation and resulting bone loss.

In combination with these discoveries, we have made great strides in understanding how an individual's own microbiome affects his or her health and disease. NIDCR continues to invest in microbiome research, supporting a database of information on oral microbes that will one day allow dentists to visualize the microbes within a patient's oral biofilm in real time—offering new tools to diagnose and treat oral disease. For example, a dentist might observe an overgrowth of a particular type of bacteria that uniquely predisposes a patient to tooth decay, and could treat that bacterial imbalance to prevent the individual from developing cavities. These emerging leads will not only guide future personalized dental treatment for millions of Americans; they will help scientists throughout biomedical research to inform better treatment approaches for other microbe-host diseases such as colitis.

TEMPOROMANDIBULAR JOINT DISORDERS

Thousands of Americans this year will be diagnosed with a painful and debilitating disorder of the jaw called temporomandibular joint and muscle disorder (TMD). Some of these individuals will recover after a single bout of TMD, while others will go on to develop chronic disease—and their healthcare providers, currently, are unable to predict the likely outcome for any individual patient. NIDCR-supported research is providing key insights that could identify people at risk for developing TMD, and predict the likelihood of progression to chronic disease. In 2006, NIDCR launched the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study. The study's latest findings present the most in-depth picture to date of the factors that may contribute to a person's developing an initial bout of painful TMD. Among the many interesting findings is that there is almost no difference in the rate at which men and women develop TMD for the first time. And yet, females are far more likely to progress to chronic TMD than males. Researchers will continue to examine potential causes of this difference, such as hormonal regulatory factors, leading to more targeted strategies for detecting and managing TMD in the future.

Although TMD specifically afflicts the jaw, OPPERA researchers found only about 15 percent of OPPERA participants diagnosed with chronic TMD have orofacial pain only. The other 85 percent have additional ailments, many of which are painful in nature, including chronic fatigue syndrome, fibromyalgia headache, and low back pain. This finding demonstrates that first-onset and chronic TMD are complex disorders that must be understood within a biological, psychological, and social model of illness. NIDCR will continue to help lead the way for all those battling these chronic conditions to find relief through a more accurate diagnosis and more personalized care.

ORAL CANCER AND HUMAN PAPILLOMAVIRUS (HPV)

When many people hear the acronym HPV, they think of its association with cervical cancer. But over the last decade, various types of this virus also have been shown to contribute to head and neck cancers. In fact, the incidence of HPV-related head and neck cancer has risen steadily over the last decade and if the pace continues, it will soon surpass the incidence of cervical cancer. This trend is particularly alarming because no effective diagnostic test currently exists to detect early HPV-related head and neck cancer. Tools are needed to screen those at increased risk of the condition and to test for possible persistence of the condition following therapy.

NIDCR will help to fill this public health need by launching an initiative to develop a viable diagnostic test. The initiative will identify DNA markers associated with HPV-related head and neck cancer, develop and validate saliva and plasma-based diagnostic tests, and evaluate and test the biomarkers in humans. Clinical studies are also ongoing to establish the safety and feasibility of administration of a DNA vaccine in certain HPV-associated head and neck cancer patients. NIDCR scientists recognize the urgency of developing innovative approaches to detect oral cancer early, when personalized treatment can be more successful, leading to better patient outcomes.

There has never been a better time to take advantage of the remarkable opportunities in science and technology waiting at our doorstep. Seizing this moment brings us closer to preventing and treating dental, oral, and craniofacial conditions as well as other diseases that share risk factors and therapeutic strategies.

PREPARED STATEMENT OF LAWRENCE A. TABAK, D.D.S., PH.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the Office of the Director (OD) of the National Institutes of Health (NIH). The fiscal year 2015 OD budget of $1,451,786,000 includes an increase of $51,033,000 above the comparable fiscal year 2014 level of $1,399,753,000.

The OD promotes and fosters NIH research and research training efforts in the prevention and treatment of disease through the policy oversight of both the extramural grant and contract award functions and the Intramural Research program. The OD stimulates specific areas of research to complement the ongoing efforts of the Institutes and Centers through the activities of several cross-cutting program offices. The OD also develops policies in response to emerging scientific opportunities employing ethical and legal considerations; provides oversight and management of peer review policies; coordinates information technology across the Agency; and, coordinates the communication of health information to the public and scientific communities. Moreover, the OD provides the core management and administrative services, such as budget and financial management, personnel, property, and procurement services, ethics oversight, and the administration of equal employment policies and practices.

The fiscal year 2015 request will also support activities managed by the OD's operational offices. OD Operations is comprised of several OD Offices that provide advice to the NIH Director, policy direction and oversight to the NIH research community and administer centralized support services essential to the NIH mission.

The functions and initiatives of the OD's research offices are described in detail as follows:

DIVISION OF PROGRAM COORDINATION, PLANNING, AND STRATEGIC INITIATIVES (DPCPSI)

DPCPSI provides leadership for identifying, reporting, and funding trans-NIH research that represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps that merit further research and would benefit from collaboration between two or more Institutes or Centers (ICs), or from strategic coordination and planning.

The Division includes major programmatic offices that coordinate and support research and activities related to HIV/AIDS, women's health, behavioral and social sciences, disease prevention, dietary supplements, research infrastructure, and science education. DPCPSI serves as a resource for the ICs and the NIH Office of the Director for portfolio analysis by developing, using, and disseminating data-driven approaches and computational tools.

The fiscal year 2015 budget for DPCPSI, including the immediate Office of the DPCPSI Director, the Offices of Portfolio Analysis and Program Evaluation and Performance, and the Office of Strategic Coordination is $11,138,000.

OFFICE OF RESEARCH INFRASTRUCTURE PROGRAMS (ORIP)

ORIP provides support for a variety of research infrastructure needs, including animal models and facilities; research models, human biospecimens, and biological materials; training and career development for veterinarians engaged in research; the acquisition of state-of-the-art and shared and high-end instrumentation; and research resources grants to expand, re-model, renovate, or alter existing research facilities. The ORIP budget for fiscal year 2015 is $275,654,000.

SCIENCE EDUCATION PARTNERSHIP AWARDS (SEPA)

The goal of the Science Education Partnership Awards (SEPA) program is to invest in educational activities that enhance the training of a workforce to meet the Nation's biomedical, behavioral and clinical research needs. The SEPA program encourages the development of innovative educational activities for pre-kindergarten to grade 12 (P–12), teachers and students from underserved communities with a focus on Courses for Skills Development, Research Experiences, Mentoring Activities, Curriculum or Methods Development or Informal Science Education (ISE) exhibits, and Outreach activities. In fiscal year 2015, the SEPA Program will be coordinated with the Department of Education to ensure that program activities are aligned with ongoing P–12 reform efforts included in the President's budget request. In fiscal year 2015, the budget for SEPAs is $18,541,000.

THE OFFICE OF AIDS RESEARCH (OAR)

OAR plays a unique role at NIH by serving as a model of trans-NIH planning and management, vested with primary responsibility for overseeing all NIH AIDS-related research. OAR coordinates the scientific, budgetary, legislative, and policy

elements of the NIH AIDS research program. OAR's response to the AIDS epidemic requires a unique and complex multi-institute, multi-disciplinary, global research program. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently, allowing NIH to pursue a united research front against the global AIDS epidemic. The fiscal year 2015 budget for OAR is $61,923,000.

THE OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH (OBSSR)

OBSSR furthers the mission of the NIH by emphasizing the critical role that behavioral and social factors play in health, healthcare and well-being. OBSSR serves as a liaison between NIH and the extramural research communities, other Federal agencies, academic and scientific societies, national voluntary health agencies, the media, and the general public on matters pertaining to behavioral and social sciences research. OBSSR's vision is to bring together the biomedical, behavioral, and social science communities to work more collaboratively to solve the pressing health challenges facing our Nation. OBSSR also coordinates and helps support the NIH Basic Behavioral and Social Science Opportunity Network, a trans-NIH initiative to expand the agency's funding of basic behavioral and social sciences research. The fiscal year 2015 budget for OBSSR is $26,094,000.

THE OFFICE OF RESEARCH ON WOMEN'S HEALTH (ORWH)

Since its creation in 1990, ORWH has worked to ensure the inclusion of women in NIH clinical research, to advance and expand women's health research, and to promote advancement of women in biomedical careers. ORWH is the focal point for NIH women's health research and works in partnership with the NIH ICs to incorporate a women's health and sex differences research perspective into the NIH scientific framework. ORWH activities are guided by the 2010 NIH Strategic Plan for Women's Health Research. This strategic plan outlines six goals to maximize impact of NIH research effort. The NIH strategic plan for women's health and sex differences research serves as a framework for interdisciplinary scientific approaches. The fiscal year 2015 budget for ORWH is $40,903,000.

THE OFFICE OF DISEASE PREVENTION (ODP)

The ODP is responsible for assessing, facilitating, and stimulating research in disease prevention and health promotion, and disseminating the results of this research to improve public health. Research on disease prevention is an important part of the NIH mission because the knowledge gained from this research leads to stronger clinical practice, health policy, and community health programs. In early fiscal year 2014, ODP released its first strategic plan. This plan outlines the priorities that the Office will focus on over the next 5 years and highlights the ODP's role in advancing prevention research at the NIH. The fiscal year 2013 budget for ODP is $5,861,000. The Office of Dietary Supplements (ODS) is within the ODP organizational structure. The mission of the ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population. The fiscal year 2015 budget for ODS is $26,786,000.

THE OFFICE OF STRATEGIC COORDINATION (OSC) AND THE COMMON FUND

OSC oversees the management of the Common Fund (CF), working with trans-NIH teams for each of the more than 30 Common Fund programs. These teams ensure that each program meets the criteria of Common Fund programs to synergize with IC funded research. The NIH CF was created by the 2006 NIH Reform Act which codified the approach of the NIH Roadmap for Medical Research to support cross-cutting, trans-NIH programs that require participation by at least two NIH ICs or would otherwise benefit from strategic planning and coordination. CF programs tackle major challenges in biomedical research that affect many diseases or conditions or that broadly relate to human health. The CF provides limited-term funding for goal-driven, coordinated research networks to generate data, solve technological problems, and/or pilot resources and tools that will stimulate the broader research community. The fiscal year 2015 budget for the Common Fund is $583,039,000.

LOAN REPAYMENT AND SCHOLARSHIP PROGRAMS

The mission of the NIH Intramural Loan Repayment Programs is to seek to recruit and retain highly qualified physicians, dentists, and other health professionals with doctoral-level degrees. These programs offer financial incentives and other benefits to attract highly qualified physicians, nurses, and scientists into careers in biomedical, behavioral, and clinical research as employees of the NIH. The Undergraduate Scholarship Programs (UGSP) offers competitive scholarships to exceptional college students from disadvantaged backgrounds that are committed to biomedical, behavioral, and social science health-related research careers at the NIH. The fiscal year 2015 budget for ILRSP is $7,145,000.

I am happy to answer any questions you may have about the OD's programs and activities as well as our plans for the upcoming year.

PREPARED STATEMENT OF NORA D. VOLKOW, M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2015 President's budget request for the National Institute on Drug Abuse (NIDA). The fiscal year 2015 budget request for NIDA is $1,023,268,000, which reflects an increase of $7,514,000 over the fiscal year 2014 level of $1,015,754,000.

The impact of substance abuse in this country is daunting; the economic toll alone exceeds $700 billion[1] a year in healthcare, crime-related, and productivity losses. NIDA strives to translate the returns of its investments in genetics, neuroscience, pharmacotherapy, and behavioral and health services research into new strategies for preventing and treating substance abuse and addiction. This scientific investment is crucial if we are to tackle rapidly evolving public health threats such as the increase in marijuana use among young people and the growing prevalence of opioid addiction and overdose deaths.

TODAY'S BASIC SCIENCE FOR TOMORROW'S BREAKTHROUGHS

There is a fundamental need to understand the complex steps of how body chemistry influences behavior and how their disruption can lead to addiction. A more detailed and personalized account of these steps will lead to a more effective and precise medicine to prevent and treat this complex brain disorder.

In this context, and thanks to recent technological developments, we've made important advances in linking genes with behavior. As a result, we now have an unprecedented capacity to screen for thousands of genetic variations and catalogue how they modulate abuse/addiction risk by influencing brain maturation, its neural architecture, and behavioral patterns. NIDA researchers are also pursuing genome and whole individual sequence analysis to identify genes that modulate addiction risk (e.g., genes that regulate drug metabolism), advancing their understanding of how environmental factors (e.g., parental style, drug exposure) can affect the expression of those genes to either strengthen or weaken behavioral patterns through epigenetic changes. The systematic identification of genetic, environmental, and neurocircuitry variations that modulate abuse/addiction risk will revolutionize our prevention and treatment capacities.

BIG OPPORTUNITIES IN BIG DATA

Big data sets are essential platforms for the analysis of complex systems in genetics and epigenetics, proteomics, brain imaging and clinical science. Vast amounts of data are being produced by the overlaying of structural and functional brain imaging information that links the molecular and cellular data with the expression of higher level brain function. A prime example is the new fMRI-based approach to generating images of the functional connectivity (FC) among brain regions in the absence of any specific task, so called resting state (rs) FC. This technique offers a powerful window into circuit-level functions that may generate behavioral responses underlying vulnerability or a diseased state. Open access to such massive databases could lead to the identification of biomarkers of psychiatric illness risk including ad-

[1] U.S.DHHS. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA, CDCP, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014; Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet. 2009 Jun 27;373(9682):2223–33; National Drug Intelligence Center (2010). National Threat Assessment: The Economic Impact of Illicit Drug Use on American Society. Washington, DC: United States Department of Justice.

diction, their trajectories, and treatment responses that could be translated for clinical use and the optimal management of patients.

Similarly, NIDA is funding the development of an open source, open framework, free National Pain Registry that collects patient demographic and treatment information from around the Nation. This information can be used to identify which pain management interventions are most effective for specific chronic pain patients and predict which patients might be at higher risk for opioid addiction. Combined with concerted efforts in the pharmacogenomics of prescription opioids, pain registries are poised to help us maximize the effectiveness of pain treatments while minimizing the likelihood of prescription opioid abuse and addiction.

NURTURING TALENT AND INNOVATION

NIDA currently supports a great deal of innovative research on drug addiction and related health problems such as pain and HIV/AIDS and will continue to be at the forefront of training the next generation of innovative researchers. The 6-year old Avant-Garde award is a good example of a program that stimulates high—impact research that could lead to groundbreaking opportunities for the prevention and treatment of HIV/AIDS in substance users. NIDA is now crafting a new kind of award, which blends NIH's Pioneer and New Innovator award mechanisms. This new opportunity, called the "AVENIR" award, is designed to attract creative young investigators to genetic research on substance use disorders and HIV/drug abuse research. Another example is NIDA's Cutting-Edge Basic Research Awards (CEBRA), designed to foster highly innovative or conceptually creative research that advances our understanding of drug abuse and addiction. The latest results of this effort include three independent studies exploring the potential benefits of neurofeedback training, transcranial magnetic stimulation, and meditation on facilitating smoking cessation.

BETTER PAIN MANAGEMENT: A MAJOR GOAL OF ADDICTION RESEARCH

Pain management is an important component of high-quality, compassionate medical care. Opioid analgesics are among the most effective medications for the management of severe pain and frequently used for pain treatment. Unfortunately, the benefits of long term opioid analgesic treatment are accompanied by significant risk of developing drug tolerance (and the need for escalating doses) and hyperalgesia (increased pain sensitivity). Exposure to potentially rewarding substances, like opioid analgesics, may reinforce drug taking behavior for persons with risk factors for addiction and trigger relapse in those that are in recovery. These are intrinsic liabilities of opioid analgesics that clearly increase the risk for diversion, abuse, addiction and overdose.

NIDA recognizes it has a critical role in ensuring the availability of safe and efficacious chronic pain management options while minimizing risk of abuse. This is why we are committed to supporting research to better predict who is at risk of addiction and to develop new classes of effective, non-addicting pain medications. Parallel to these efforts, NIDA is proactively pursuing methods to minimize the risk of overdose with existing medications. For example, NIDA and Lightlake Therapeutics Inc. have partnered to develop an intranasal delivery system of naloxone (an opioid receptor blocker that can rapidly reverse the overdose of prescription and illicit opioids), which could greatly expand its availability and use in preventing opioid-related deaths, a public health problem of epidemic proportion in the U.S.

HEALTH CONSEQUENCES OF MARIJUANA USE

There is a dangerous and growing misperception that marijuana use is harmless, resulting in its status as the most commonly used illicit drug in the United States with about 12 percent of people aged 12 and over reporting use in the past year.[2] Marijuana use has been associated with significant adverse effects, including addiction, cognitive impairment and car accidents. The key to minimizing negative outcomes lies with the intensification of our efforts to educate the public about the dangers of marijuana use and, with the deployment of multipronged, evidence-based strategies to prevent and treat the abuse of and addiction to marijuana and other drugs. To meet this challenge, NIDA has released several funding announcements to encourage research on the impact of changing marijuana policies; and, in partnership with other NIH institutes, is planning a large-scale, prospective study that fol-

[2] Substance Abuse and Mental Health Services Administration, Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H–46, HHS Publication No. (SMA) 13–4795. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.

lows children prior to drug use into early adulthood to determine whether and how marijuana and other commonly used substances (e.g., alcohol, tobacco) affect the developing brain.

MEDICATIONS DEVELOPMENT

Our current approaches to develop next-generation pharmaceuticals take advantage of new technologies using immunotherapeutic or biologic (e.g., bioengineered enzymes) approaches for treating addiction. The goal is to develop safe and effective vaccines or antibodies that target specific drugs, like nicotine, cocaine, and heroin, or drug combinations. If successful, immunotherapies—alone or in combination with other medications, behavioral treatments, or enzymatic approaches—stand to revolutionize how we treat, and maybe even someday prevent addiction.

CONCLUSION

The field of addiction research continues to benefit from the explosion in genetic knowledge, the advent of precise technologies to probe neuronal circuits, and the emergence of openly accessible big data platforms. NIDA's research is strategically poised to take full advantage of these and other emerging opportunities to develop the knowledge base that can be used to reduce drug use in this country.

PREPARED STATEMENT OF JACK WHITESCARVER, PH.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for fiscal year 2015 for the trans-NIH AIDS research program, which is $3,004,973,000. This amount is $19,882,000 above the fiscal year 2014 enacted level of $2,985,091,000.

The authorizing law requires that the Office of AIDS Research (OAR) function as "an institute without walls" and allocate all dollars associated with this area of research across the NIH. Therefore, the total for AIDS research includes both extramural and intramural research (including research management support, management fund, and service and supply fund), buildings and facilities, training, and evaluation, as well as research on the many HIV-associated co-infections and comorbidities, including TB, hepatitis C, and HIV-associated cancers. It also includes all of the basic science underlying this research. Other disease areas are not reported this way. Therefore the total for AIDS-related research is not comparable to spending reported for other individual diseases.

NIH AIDS RESEARCH ACCOMPLISHMENTS

In the three decades since AIDS was first reported, NIH continues to be the global leader in research on HIV and its many related conditions. New avenues for discovery have been identified, providing possibilities for the development of new strategies to prevent, treat, and potentially cure HIV. Recent accomplishments include:

—Development of new treatments for many HIV-associated co-infections, comorbidities, malignancies, and clinical manifestations;
—Development of new strategies for the prevention of mother-to-child transmission;
—Demonstration of the first proof of concept that a vaccine can prevent HIV infection and identification of potential immune markers for protection;
—Discovery of more than 20 potent human antibodies that can stop up to 95 percent of known global HIV strains from infecting human cells in the laboratory;
—Demonstration that the use of antiretroviral therapy by infected individuals can dramatically reduce HIV transmission to an uninfected partner; and that the use of antiretroviral drugs by uninfected individuals can reduce their risk of HIV acquisition;
—Discovery that genetic variants may play a role in enabling some individuals, known as "elite controllers," to control HIV infection without therapy; and
—Advances in basic and treatment research aimed at eliminating viral reservoirs in the body that for the first time are leading scientists to design and conduct research aimed at a cure for HIV/AIDS.

In just the past several months, NIH intramural and extramural researchers have produced a number of exciting new advances. NIH researchers published the results of studies utilizing potent human neutralizing antibodies that successfully suppressed a form of HIV in primates. This important research could potentially result in a new form of treatment for HIV that could be used as an adjunct to antiretroviral therapy and could lead to opportunities for novel research to treat and potentially cure HIV. NIH-sponsored researchers also have made tremendous

strides in producing and analyzing proteins that may provide an important new pathway in AIDS vaccine design.

A team of NIH-funded investigators recently reported the first case of a newborn in Mississippi who was "functionally cured" of HIV infection. The infant received antiretroviral therapy immediately after being diagnosed at birth but was then lost to follow-up and treatment. The now nearly three year-old child has re-entered care with no indication of HIV disease and no detectable virus in the absence of therapy. Additional studies are under way to better understand this case and may lead to clinical trials to see whether a similar approach could be used to achieve a "functional cure" for other HIV-infected newborns. NIH is leading global research efforts to capitalize on all of these advances, move science forward, and begin to turn the tide against this pandemic.

THE AIDS PANDEMIC

Despite this progress, the HIV/AIDS pandemic will remain the most serious global public health crisis of our time until better, more effective, and affordable prevention and treatment regimens—and eventually a cure—are developed and available around the world. UNAIDS reports that in 2012, more than 35 million people were estimated to be living with HIV/AIDS; 2.3 million were newly infected (half of them women); and 1.6 million people died of AIDS-related illnesses.

In the United States, HIV/AIDS continues to be an unrelenting public health crisis, disproportionately affecting racial and ethnic populations, women of color, young adults, and men who have sex with men. The Centers for Disease Control and Prevention estimates that approximately 1.1 million people are HIV-infected; approximately 50,300 new infections occur each year; and one in four people living with HIV infection in the U.S. is female.

COORDINATED TRANS-NIH AIDS RESEARCH PROGRAM

The NIH AIDS research program is coordinated and managed by the OAR, and carried out by nearly every NIH Institute and Center (IC). Through its unique trans-NIH planning, budget, and portfolio review processes, OAR identifies the highest priority areas of scientific opportunity and ensures that precious research dollars are invested effectively. Scientific priorities for AIDS research are constantly reassessed and reflected in the budget. The annual trans-NIH AIDS strategic plan, developed by OAR in collaboration with both government and non-government experts, guides the development of the trans-NIH AIDS research budget. Each year, the state of the science is reviewed, newly emerged and critical public health needs are assessed, and scientific opportunities are identified. This annual process culminates with the identification of the highest strategic priorities and critical research needs. OAR develops each IC's AIDS research allocation based on the Plan, scientific opportunities, and the IC's capacity to absorb and expend resources for the most meritorious science——not on a formula. This process reduces redundancy and ensures cross-Institute collaboration. The fiscal year 2015 budget request reflects the priorities of the fiscal year 2015 strategic planning process.

AIDS RESEARCH PRIORITIES AND OPPORTUNITIES

The advances made by NIH investigators have opened doors for new and exciting research opportunities to answer key scientific questions that remain in the search for strategies to prevent and treat HIV infection both in the United States and around the world. The fiscal year 2015 budget priorities are:

—Basic research that will underpin further development of critically needed prevention methodologies, including vaccines;

—Innovative multi-disciplinary research and international collaborations to develop novel approaches and strategies to eliminate viral reservoirs that could lead toward a cure for HIV;

—Research to develop better, less toxic treatments and to investigate how genetic determinants, sex, gender, race, age, nutritional status, treatment during pregnancy, and other factors interact to affect treatment success or failure and/or disease progression; and

—Studies to address the increased incidence of co-morbidities, including AIDS-associated malignancies; cardiovascular, neurological and metabolic complications; and premature aging associated with long-term HIV disease and antiretroviral treatment.

SUMMARY

The NIH investment in AIDS research has produced groundbreaking scientific advances that have benefited not only patients with HIV, but those with other diseases as well. For example, the development of protease inhibitors to treat HIV has led to development of a new drug combination that can cure hepatitis C, which affects about 150 million people globally. That advance in hepatitis C research may, in turn, provide important knowledge toward an HIV cure. Drugs developed to treat HIV-associated opportunistic infections are benefiting the more than 28,000 Americans who receive an organ transplant each year. Research on HIV-associated neurologic and cognitive manifestations ultimately will benefit millions of patients with Alzheimer's disease and other aging and dementia issues.

Despite these advances, however, AIDS is not over, and it is far too soon to declare victory. Serious challenges lie ahead. The HIV/AIDS pandemic will remain the most critical public health crisis of our time until improved and affordable prevention and treatment regimens are developed and universally available. NIH will continue to search for critical solutions to prevent, treat, and eventually cure AIDS.

Thank you for your continued support for these efforts.

Senator HARKIN. Thank you very much, Dr. Collins. We will start a round now of 5-minute questions. As I said at the NIH, I have never come away from a conversation or listening to you, Dr. Collins, without being more enlightened and more hopeful about the future. I like that "National Institutes of Hope."

Let me just ask you a question about the BRAIN Initiative, if I can start with that. I have got two or three questions on the BRAIN Initiative. Paint for me a picture of how you see the research going ahead in the BRAIN Initiative. And we have some partners, four outside partners, right now that are also putting money into this, and you have an advisory group from DARPA (Defense Advanced Research Projects Agency) and NSF (National Science Foundation). Paint for me the picture of how you see this developing in the next 2, 3, 4, 5 years. And sort of what do we hope to get from this?

BRAIN INITIATIVE

Dr. COLLINS. Well, we are enormously excited about this, and I am going to ask my colleague, Story Landis, who is a major leader at NIH in the BRAIN Initiative, to say a word. But just very briefly from my perspective, this is one of those moments that comes along once in a long time where the technology to be able to tackle a truly important problem, understanding how the circuits in the human brain work, has arrived at the point where we have this kind of push, bringing disciplines together that have not necessarily found each other, and making this a priority. We believe we can transform our understanding of this incredible organ with its 86 billion neurons, each of which has maybe a thousand connections. But, Story, say where we are and where we are going.

Dr. LANDIS. So we are very excited about the opportunity to really understand how neural circuits in the human brain work—86 billion neurons, each of which are connected in complicated circuits and pathways that process information, that allow us to see an image and interpret it, to hear words and understand what they mean, to remember, to reason.

We have some understanding now of how those 86 billion neurons are organized into circuits, but we do not nearly have enough detail, and we do not know enough about how information is processed. And the goal of the BRAIN Initiative in the first five or so

years is to really develop the tools that will allow us to probe those questions. There will be early on potential opportunities to translate to disease, and I could give you some examples if you would like.

Senator HARKIN. Let me ask you this, Dr. Landis. Are you working with the National Institute on Aging? Is there any connectivity between the BRAIN Initiative and Alzheimer's research?

Dr. LANDIS. Absolutely, although the understanding that we will gain from the BRAIN Initiative will then be applied to understanding how circuits are perturbed in Alzheimer's. Alzheimer's disease nerve cells die. We would like to prevent that death, but in the absence of tools yet to do that, the circuits reorganize when cells are lost. And the BRAIN Initiative will give us a better understanding of why that reorganization occurs and how we can potentially use the neurons that remain to have much more function.

Senator HARKIN. Well, I asked that because, you know, we have a lot of things confronting us in the future. I will get to Dr. Varmus and cancer. But if we do not do something about Alzheimer's, that is a tsunami that is going to hit us big time. And so I just really wanted to get that on the record that the money that we are putting into the BRAIN program, BRAIN research program, also has a connectivity to Alzheimer's research.

Dr. LANDIS. Absolutely.

Senator HARKIN. Okay.

Dr. COLLINS. Think of the BRAIN Project as a foundation for all neurological diseases, just like the Genome Project was a foundation for all genetic diseases. It lifts all of those boats of research to go higher and faster.

Senator HARKIN. Sure.

Dr. LANDIS. And psychiatric diseases and drug abuse, all the brain disorders.

FUTURE OF CANCER RESEARCH

Senator HARKIN. Exactly. Dr. Varmus, again, I would be remiss if I did not thank you for a lifetime of devotion and dedication to biomedical research, stewardship of the NIH for a lot of the time I was either chairman or ranking member. And it is good to have you back as the head of the National Cancer Institute.

Here is my question: What excites you the most right now? In all of cancer research and stuff, what is it that gets you up in the morning right now that you are looking ahead to do?

Dr. VARMUS. Thank you. And before I give you a brief answer to that question, let me first of all compliment you on your service. You and I have been facing each other across the dais like this for 20 years off and on, and I have always admired your passion, your commitment to the NIH, your honesty. And even on those rare occasions when we disagreed on a few issues, we have had a collegial and constructive relationship. And your departure from this Congress is a heavy blow to the NIH and to its supporters.

Senator HARKIN. I appreciate that.

Dr. VARMUS. What most excites me at the moment is the deep intellectual understanding we have about how cancer arises and how the body tries to respond to it. And the connection between

basic science and its very near apposition to what we can do practically is thrilling.

Over 40 years ago, I have to confess when I began doing cancer research, the application of what we were trying to learn with chicken viruses and mouse viruses was very far away. Today we use tools of genomics and immunology and biochemistry in a way that is very closely connected to what we are doing in the clinic. So when we discover a new gene that is involved in cancer, it is not long before we find some drug, perhaps an existing drug, that can be applied to patients whose tumors are being analyzed with the instruments of genomics to identify exactly what is wrong with that cancer, and to carry out in a precise fashion a clinical trial that is designed in entirely new ways.

Similarly, we have learned from basic immunology the kind of thing that Dr. Collins just illustrated is also being applied in immediate ways to try to interfere with the breaks on the immune system that have kept the immune system from attacking cancer cells.

Senator HARKIN. My time has run out, but I will have a follow-up on that on immunotherapy and Dr. Rosenberg and what he is doing out there. Okay.

Senator Moran.

ALZHEIMER'S DISEASE

Senator MORAN. Mr. Chairman, thank you very much. Dr. Collins, Dr. Landis, and others, thank you very much for attending the recent hearing we had in regard to Alzheimer's in particular. Several members asked that day if we would reach the goal of a cure for Alzheimer's by 2025 and how much money it would take to do so.

I understand how difficult it must be to quantify such an answer, but I think it is important for us to know if our Alzheimer's research funding is on track. Therefore, I am looking for your professional opinion or opinions as to how much money does NIH need in fiscal year 2015 to keep pace with the goal of a cure for Alzheimer's by 2025.

Dr. COLLINS. Well, thanks for the question, Senator, and that was an excellent hearing that was held by this subcommittee. And we had a great opportunity there to look at the challenge and also the scientific opportunities, which are really coming forward in very exciting ways, recognizing that the challenge here in terms of both the economic and human cost of this disease can hardly be overstated.

As you have pointed out, we have an action plan for Alzheimer's disease, part of the legislation that put in place this project—plan. And the National Institute on Aging, directed by Dr. Hodes, has been deeply engaged in that, running a research summit at NIH, and polling the entire community about where the research opportunities would be. It is wonderful that in fiscal year 2014, largely due to this subcommittee's efforts, $100 million has been appropriated for the National Institute on Aging, the bulk of which will be put into promising Alzheimer's research.

I have looked carefully at the way in which the Alzheimer's plan maps across the various years. As you know, science tends not to operate in 1 year intervals. Many of the components of the plan are

more in a 3-year kind of timetable. I could show you a Gantt chart that goes on for many pages about how each of these components might start and hopefully reach a milestone.

It is very difficult, though, with all the multiyear aspect of this to say, well, what do we need exactly in fiscal year 2015? And I have sort of tried with Dr. Hodes to come up with that kind of estimate, and I am afraid it would not be a reliable one. Part of that is, of course, we do not have the ability in science to know exactly what is going to happen next month or the month after that. And a lot of the research in Alzheimer's is being developed by investigators out there in our wonderful brain trust, the universities that are doing this research. And we might wake up tomorrow and find that something has happened that completely changes the direction we want to go. So while this plan is a good one to work with, it will undoubtedly evolve over time.

So I know I am sounding like I am not giving you an answer, and I guess I am trying to say I think to put a dollar figure right now on fiscal year 2015 would be to overstate what I really can predict to be necessary for this purpose. Again, we are thrilled with $100 million in 2014. We were delighted to see in the President's Opportunity, Growth, and Security Initiative another $100 million would come to Alzheimer's disease should that become possible.

Senator MORAN. You have the capability, Dr. Collins, I assume, of telling us or telling me that the $100 million in fiscal year 2014 was not too much.

Dr. COLLINS. It was not too much. You are quite right about that. And, you know, you are asking about Alzheimer's. You could be asking about many other areas of NIH research as well, and I would tell you we do not have too much money to work on anything that we are working on. We are not limited by ideas. We are limited by resources, whether it is cancer, infectious disease, heart disease, whatever. That is our current state.

Senator MORAN. Doctor, let me take this question in a broader step. But first let me say that my expectation would be as those scientific developments occur, a reason that we should have the kind of hearings that we have on an ongoing basis is so that you can then come to us and say this development has happened in some university in the country or here at NIH. And, therefore, if you would invest additional dollars in this area, we believe we can advance the outcomes more quickly.

And so, my continued effort, I think, will be to try to get you to help us prioritize spending based upon science, based upon success in research where we ought to put the dollars that we have to allocate within the 27 Institutes and Centers that you and NIH engage in.

Dr. COLLINS. Senator, I would welcome those kinds of conversations at any time, and appreciate your leadership in that kind of planning process.

DISEASE SPECIFIC FUNDING

Senator MORAN. I have 28 seconds left for a follow-up question, which is this: You have—you, NIH—has historically opposed disease-specific funding. You want the allocations to occur based upon science, not on politics, and I certainly share that goal. If we are

underfunding in an area of research—if we start with low funding in a particular area of research, it is harder to have the developments that then allow you to come to us and say we have had a breakthrough, we need more. We need to accelerate the funding of that research.

How are you—I mean, can you give me examples—I do not have the history that Senator Harkin has, but does it happen from time to time in which you come to Congress and say we need to prioritize the research in this area, and are you willing then to tell us that we reduced the priority someplace else? How do we ever get into the circumstance in which any of us are willing to say our money should go into this basket, knowing that it is not infinite? The money has to come out of some other basket.

Dr. COLLINS. Well, again, I appreciate the question. And this is the kind of conversation we have around the table at NIH all the time with the 27 Institute and Center directors, each of whom has a strategic plan that they are constantly refreshing and revising.

The good news is that the boundaries between those institutes are very porous. And if we collectively identify an opportunity that demands additional investments in a particular direction, we often can figure out how to do that without having to go through a long lead time to try to adjust a future year's budget. And we are quite capable of doing so.

And increasingly, that is a good thing because the next breakthrough in cancer might come from the Diabetes Institute, and the next breakthrough in infectious disease might come from the Center that is looking at translational sciences. So we are really, more than we ever have been, a unit, a whole here that thinks about biomedical research collectively, not in a series of buckets.

Senator MORAN. Thank you very much.

Senator HARKIN. Thank you, Senator Moran. And our distinguished Chair of the entire Appropriations Committee, who happens to have a real interest in NIH, I can tell you that.

Senator Mikulski.

Senator MIKULSKI. Thank you very much, Senator Harkin, and we are so glad that you are holding this hearing. And I think it shows the significance of the way we think about the National Institutes of Health, which we all affectionately and with great admiration do call the National Institutes of Hope. The fact that Senator Shelby is here, the vice chairman of the Appropriations, and myself shows our commitment to really trying to make sure that NIH has the resources it needs to continue to be the premiere global agency for biomedical research, and to do it on a bipartisan basis.

I know you spoke earlier, if I could. You were kind of emotional about this hearing, and I am emotional about this hearing for you. I recall coming to the United States Senate. I was sworn in 1987, working with then the beloved Nancy Kassebaum, you, and Ted Kennedy, when women were not even included in the protocols, many of the research things, at NIH. There were many reasons. Many were just flawed sociology rather than good biology.

Imagine in those years when we were not even included, and then we advocated for the Office of Women's Health. The funding then for breast cancer was quite spartan and skimpy. Again, we

turned to you. And then as we made steady advances, George Herbert Walker Bush appointed Bernadine Healy to be the head of NIH. Dr. Healy also reached out again to us to ask us to look for a famous longitudinal study on hormone therapy. That hormone therapy study resulted in the change in the way hormones are treated in terms of hormone therapy for women, and it resulted in breast cancer coming down by 15 percent.

I recall with great emotion my last call with Bernadine Healy, and this is what she said. I called her, and there was an article in the New York Times, Dr. Varmus, that said breast cancer rates have come down 15 percent. And I said, "My god, Bernadine, can you believe that?" She said, "Yes, Barbara. Can you believe because we worked together we are saving lives a million at a time?"

That is what we are trying to do here with this hearing. We are trying to look at these issues. And I am going to say to you, Senator Harkin, the Catholic nuns had a phrase when they taught people like me. They had a phrase in Latin called "exegi monumentum aere perennius aedificabo." It means we will build a monument more lasting than bronze. I feel our monument to you, to both you, to Senator Specter, to Bill Frist, Ted Kennedy, is the way we walked across the aisle is to build a monument more lasting than bronze, and that is to make a significant public investment this year in the National Institutes of Health to get it right back on track to where it was, and to have a steady growth plan of action so that at the end of the day, at the end of the year, at the end of our terms, we know that we have been working together to save lives a million at a time. So I want to just shake your hand and thank you. And, Moran, you are from Kansas.

Senator MORAN. Yes.

Senator MIKULSKI. You know what Nancy did shoulder to shoulder here. Senator Shelby has been a great advocate.

I have many questions that I am going to ask. We could hold a hearing on each and every one of those people—distinguished people here. We are lucky to have them. Their combined years of service are stunning. Many of them at this table could be in such lucrative careers in the private sector.

I remember working with Dr. Fauci when there was this unknown disease in which men were dying all over the country. It was called AIDS. A little boy named Ryan White came here with his mother when he had been targeted by his classmates for taunts and isolation. Now look at where we are. We could take item after item, issue after issue, and it really shows what we need to do.

So we need to not only fund the research, we need to support the people who do the research. And to those young people out there right now thinking about careers that there is hope in trying to find cures to give people hope. And so, this is where we really need to work on a bipartisan basis, hands across the aisle, hands across the dome. And I think we can make a significant difference. So we want to help build a monument more lasting than bronze.

I yield back my time.

Senator HARKIN. Thank you very much. That was a very poignant statement, and I thank you for that. The only thing I would add is we have to come to grips with the funding, and I am open for any and all suggestions.

Senator MIKULSKI. I know we are all going to get into this.

Senator HARKIN. I just met yesterday with a couple of people who had an interesting idea on funding for translational science. Gordon Gund and Karen Petrou from the Foundation for Fighting Blindness have come up with—I do not need to go into that now, but there are ideas being spawned out there on how we might raise more money for NIH. So anybody that has got suggestions, we need to keep looking.

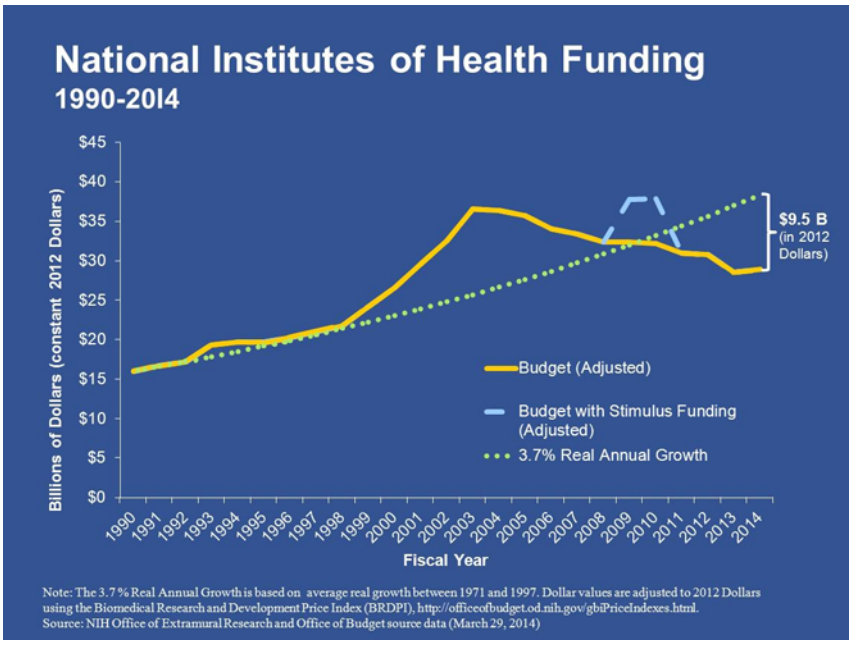
PREFERRED METHOD OF FUNDING

Senator MIKULSKI. And, Mr. Chairman, if I could, if Dr. Collins could comment. We had a great hearing on Alzheimer's, and also that is an epidemic in our country, as is autism, quite frankly. And again, many here could comment on it. And then there are those things that seem benign and not too scary, but then along comes flu. But when we look at the "A" words—autism—there was talk of, like, do we need, like, a Manhattan Project.

And I wonder to Dr. Collins and the esteemed panel, what is it that is the best thing for NIH, sustained, steady growth with kind of an agreement across the aisle and across the dome of steady increases to the way we had the concept of—I understand if we added—kept pace with inflation at 3 percent, and then another 5 percent, we could get to almost doubling NIH—we do not want to use that phrase anymore—to $40 billion. Is that better rather than a concentrated big buck expenditure on one particular area for——

Dr. COLLINS. I really appreciate the question. And I wanted to show you a graph——

[The graph follows:]



Senator MIKULSKI. In other words, does the idea of a Manhattan like project really have efficacy, or does it sound good, but——

Dr. COLLINS. What you see on the screen here is the projection over the past years since 1990 of the NIH support corrected for inflation because we have to deal with that. That is the yellow line. You see the blue bar is there for the Recovery Act, those 2 years of an increment which helped with sort of pent-up need.

But notice the doubling, which happened there between 1998 and 2003, then encountered essentially flat budgets, which inflation has eroded ever since. And you can see interestingly, the dotted line is the trajectory we were on before the doubling, which if you go back to 1970, we were on a period of about 3.7-percent annual growth. If we had stayed on that steady trajectory, we would now be $10 billion almost higher than we are. Very interesting to sort of contemplate this.

Now, the doubling was wonderful. The doubling did huge things for biomedical research. But what came after has been really quite painful. And to answer Senator Mikulski's question, the worst thing you can do, I think, to biomedical research is to create an area of uncertainty, of ups and down, of a roller coaster. Science operates not as a spring, but a marathon. You need confidence that there is going to be support there so that young scientists can tackle really innovative risky projects. And this up and down circumstance now hitting historic lows in terms of opportunities to get support is really quite damaging.

And what would be vastly better, Senator, would be for us to be able to count on a more or less stable trajectory of inflation plus some percentage that you could be fairly confident was going to be maintained. I understand how hard that is in the current fiscal situation, but if you are asking my judgment about what NIH needs in order to flourish and in order to contribute to this Nation what we think we can contribute and to the world, that would be it, that kind of steady trajectory that you could be confident in.

Senator HARKIN. Thank you, Dr. Collins. Senator Shelby, our ranking member of the entire committee. Used to be the ranking member of this subcommittee.

Senator SHELBY. Thank you. Thank you, Chairman Harkin, and thank you for all your service here and advocacy for NIH. I believe as a veteran member of the Appropriations Committee looking at all the aspects of the various requests for money that the NIH, I think, by far is the best investment we have made. And we should make sure that it is properly funded and not let it be eaten up with inflation.

ECONOMIC IMPACT OF BIOMEDICAL RESEARCH

Dr. Collins, tell us the economic impact of biomedical research, including pharmaceutical research—NIH is the leader, but going on elsewhere, too, in the private sector—in this country, and how important is it not to just our health, but to our economy and our leadership in the world. You have some numbers there?

Dr. COLLINS. I have some numbers. I could go on all day with numbers because——

Senator SHELBY. How about taking a few minutes?

Because the chairman will gavel——

Dr. COLLINS. I will try to rein it in here.

Senator SHELBY. Thank you.

Dr. COLLINS. I will tell you when I came to this job to be Director of NIH, I did not realize how important it was going to be to have this kind of case in front of the public and in front of the Congress in order to justify what we are doing because the main reason I am excited about being at NIH is the advances in research that are going to help people. But there is another great story here, which is that every $1 that we give out in grants to all 50 States, by most estimates, returns more than two-fold in terms of economic——

Senator SHELBY. It is a huge multiplier, is it not?

Dr. COLLINS. It is about $2.21 per $1 according to one——

Senator SHELBY. In GDP (gross domestic product) and jobs, right?

Dr. COLLINS. And in jobs. We directly support about 432,000 jobs through our grants. But if you figure out how NIH is sort of part of the ecosystem that creates jobs in biotech and in pharma, the estimate is something like 7 million jobs are dependent upon the progress that NIH makes, and are somewhat jeopardized by our current circumstance.

And when you look at the competition issue, which is another one that people raise, certainly America has led the world in biomedical research for the last 20 or 30 years, but that is gradually eroding, and, in fact, eroding more quickly these days, especially after sequester. And if we are interested in seeing those kinds of returns like were talked about with the Genome Project, a 141 to 1 return on those dollars, do we really want those returns to go somewhere else, or do we want them to happen right here?

AUTOIMMUNE DISEASES

Senator SHELBY. Absolutely not. We want to keep it here. Let me ask you a question. I am limited in time. We have a chairman with a good gavel here. In the autoimmune area that I have worked with you before, rheumatoid arthritis and lupus, are you cutting back on the money there? It seems like you are. And if so, why?

Dr. COLLINS. We are only cutting back because we have to cut back everywhere.

Senator SHELBY. Because of lack of money.

Dr. COLLINS. Even with the wonderful things you all did with the fiscal year 2014 omnibus, we did not recover everything we lost in the sequester. I will say one bit of good news about lupus is the development of this partnership with industry called the Accelerating Medicines Partnership, AMP, because lupus is one of the targets that we are going after.

Senator SHELBY. They are kind of matching you on money, right?

Dr. COLLINS. They are, $230 million over 5 years, half of it from us, half from them, and bringing scientists around the same table who would not normally be talking to each other, and having this all done in an open access fashion. This is an interesting experiment, but it may very well get us that next generation of drug targets for lupus.

Senator SHELBY. Doctor, how important is not just for lupus, but all the autoimmune diseases—the whole spectrum affects so many of the areas of research that you are working on, does it not?

Dr. COLLINS. Absolutely, and maybe Dr. Fauci would want to say a word about this since he is the most distinguished immunologist in the room.

Senator SHELBY. We know.

Dr. FAUCI. Thank you for the question, Senator. Indeed, I think the issue with autoimmunity is really an example of how fundamental basic research and understanding how the immune system is regulated over the last several years have provided extraordinary insight into how we can better manage, diagnose, and ultimately treat, and in some cases even prevent, autoimmune diseases.

Whenever you think about autoimmunity, the terminology itself is descriptive, namely an immune response against oneself that is inappropriate, and that is what is studied at the very basic level. At the NIH, we now are developing consortia where, as you hinted, multiple institutes are involved in immunology—the Cancer Institute, the Heart, Lung, and Blood Institute, our institute, the Arthritis Musculoskeletal and Skin Diseases Institute, et cetera. They all are, and we have a consortium now——

Senator SHELBY. Immunology kind of transcends it all, does it not?

Dr. FAUCI. It is one of those disciplines that essentially touches to a greater or lesser degree virtually everything we do.

CYSTIC FIBROSIS

Senator SHELBY. Dr. Collins, in another area—my time is limited, just a few seconds—but cystic fibrosis. We have come a long way there. We are a long way from a cure, but we have extended a lot of the children's lives, you know, beyond, gosh, what we thought. Where are we today, and what are some of the hopes there?

Dr. COLLINS. Well, cystic fibrosis is a wonderful example of how knowing the molecular basis of a disease can get you to a point with a great deal of hard work to a targeted therapeutic that is not just hoping something will work, but designing it to work.

So cystic fibrosis, where my lab had the privilege of being involved in that and found the gene in 1989. Just a year ago, the first really effective therapeutic for about 5 percent of cystic fibrosis patients that have a particular mutation in that gene was approved by the FDA, infact. And it is truly dramatic the stories you hear from those individuals. I have heard stories of kids who were on the lung transplant list who are now not on it anymore.

The main challenge now is to find an equivalent therapy for the majority of cystic fibrosis patients that have a different mutation, the so-called Delta F508, and there is a clinical trial very actively underway by Vertex. The drug is called VX–809. We are all holding our breath to see what the results of that will look like. The initial glimpse with a smaller phase two study looked pretty promising.

So you have gone—it took a long time. And one of the things that NCATS, and my colleague here, Dr. Austin, is charged to do is to try to shorten what would be a 20-year timetable into something much faster. But the pathway here that was charted by cystic fibrosis in a collaboration with the CF Foundation that was a major

partner here is truly exciting. It is a paradigm. We could do this again.

Senator SHELBY. Thank you very much for the work you do. Thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Shelby.

Senator Kirk.

REHABILITATION STANDARDS

Senator KIRK. I want to ask Story a question as a stroke survivor. We have two members—senators on this committee who are stroke survivors. I would like to take you into the world of our rehab standards, which Senator Johnson and I have both introduced legislation, S. 1027, to speak on behalf of the 900,000 Americans who will survive stroke we expect this year. We know that roughly one-third of them will never return to work. And Tim Johnson and I have a belief that we could set a national standard of returning those stroke survivors to work. That would unlock a hell of a lot of Americans to pay taxes and be productive.

Let me just burrow in for rehabilitation standards. My understanding is out of the $3 billion NIH, about $66 million is spent. I think the country would do well to have NIH establish a rehabilitation standard.

Dr. LANDIS. So, NINDS (National Institute of Neurological Disorders and Stroke) recently established a stroke network of clinical centers that will undertake stroke trials. And one of the major reasons we did this was to have a balance in our investment in prevention, acute treatment, and stroke rehabilitation. We have recently finished one trial, which has shown that it is not—never too late to start rehabilitation for stroke, that significant gains can be made even after 6 months. We have another trial underway. But this has clearly been an area where there has not been sufficient investment, and this clinical trials network will enable us to do more trials better and faster, which will create the kind of standards that you are asking for.

Dr. COLLINS. Could I add one thing, that the number you mentioned is the funding for the National Center for Medical Rehabilitation Research, NCMRR, which is actually within the National Institute of Child Health and Human Development. But that is not the sum total of all that we spend on rehabilitation research. Much of what Dr. Landis was just talking about is in a different part of the budget. So the total expenditures on rehabilitation research are several times that number, just to clarify.

JOHN PORTER MEMORIAL

Senator KIRK. Thank you, Mr. Chairman. I just wanted to—could I follow up and thank you for honoring my political mentor, Congressman John Porter, the other day, the man who on a bipartisan level led to the doubling of funding for this institution. You guys honored a great man who really put together an awesome team with Speaker Gingrich on that.

Dr. COLLINS. And, Senator, let me thank you for sending a wonderful video that the 400-some people who were there for that dedication watched and were touched by. And I appreciate very much your contributing to our event. This was a grand moment for NIH.

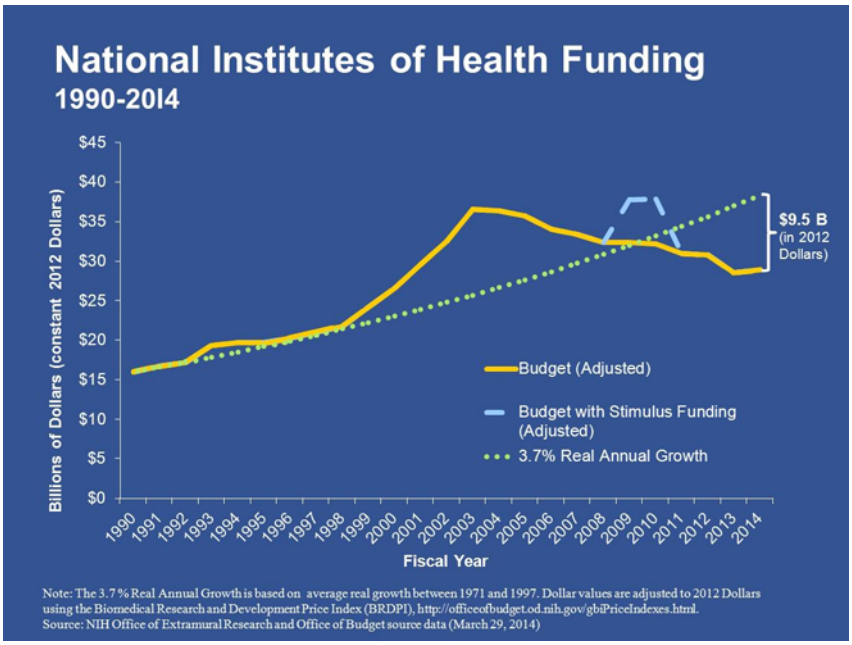
Let me say one other thing about rehabilitation research. We are very much in the process now of seeking a new director for this National Center for Medical Rehabilitation Research, someone who will be particularly forward looking in identifying opportunities, how to work with the institutes, how to build the case here for rehabilitation research to be even more vigorous than it has been. And we are looking for the very best person on the planet to do that.

Senator HARKIN. Thank you very much. We will start another round.

FUNDING HISTORY AND SUCCESS RATES

Dr. Collins, do you still have that chart that showed where that doubling was? You showed that line for the constant inflationary increase of, I think it was $3.7 or something. That one right there.

[The graphic follows:]



Senator HARKIN. Again, just for the record—there may be people who were not here at that time. Here is how we came about that doubling. In the 1990s, we saw the rate of approval of grants percentage going down and down and down from what it had been in the 1980s.

And so, meeting with people at the Institute then—it was Dr. Varmus at that time, if I remember right, others. We were talking about what would it take to sort of get back up to that level where we were in the 1980s for the percentage of—what is the phrase I am looking for—grant approvals, right?

Dr. COLLINS. Success rate. Success rate.

Senator HARKIN. Yes, success rate. And so, we got that. And what that would take would be—what it meant was to double the funding over a period of 5 years. Our thought was that once we did that and got up there, that blue would then start up there where the top was, and we would go on——

Dr. COLLINS. That is what we were hoping for, too, believe me.

VOICE. The soft landing.

Senator HARKIN. This was never meant as some transitory type of a funding bump. Now, maybe the Recovery Act was. That was sort of a transitory bump, but the doubling was to get us back up to that level and then continue on.

Dr. COLLINS. Yes.

Senator HARKIN. And so, we sat here through the 2000s and saw what happened. Again, I do not mean to speak politically, but just factually. We had two wars going on. 9/11 had happened. More and more money was being siphoned off for that. I am not making a judgment call on that. That is just what happened. And we were in a situation where we were not raising revenues, but more and more money was going for the War on Terrorism, and that is what happened. We just did not have the resources, and we came back down, and that is where we are today.

It pains me, and it pains a lot of people to think that that happened. We deliberately did that to get that line back up there and to keep it going. And, well, other things happened, and so we are back in this situation now, and we are scrambling to find the resources that we need to do this. We need more revenues. That is just my own thing. We need revenue. I think the taxpayers of this country would not mind paying a little bit more in their taxes or the wealthy or the corporations, everybody, to know that this was going to help NIH and that is where the money was going.

And so, somehow we have just got to get the revenues in for this, and like I said, I am open for any other thoughts and suggestions on how to do it. Senator Hatfield at one time had an ingenious idea of doing that. I joined him in that. That did not get very far, but it was a proposal that we would take, I think it was 1 cent out of every $1 that went for healthcare premiums. See, a lot of people do not know that when you go to a drugstore and you buy a prescription, and when you get a prescription drug or something like that, some of that money goes for research. But we do not do that in our healthcare policies. When you buy a healthcare policy, none of that goes for research.

So the idea that Hatfield came up with was that 1 cent out of every $1 that would be—go into a fund that would come to this committee. That would go to NIH as long as we funded NIH at last year—at the previous——

Senator MIKULSKI. Maintenance of effort.

Senator HARKIN. Maintenance of effort, thank you. That phrase, "maintenance of effort," then that money would be available to NIH. That would have been a great deal to have, but we did not get it. And I am still thinking that there is something out there in that realm of healthcare policies where people who are buying healthcare policies would say, "Yes, I would like to have a half a penny or something go to biomedical research and come into a fund." I think people would support that if they knew that is where

it was going. It was going to NIH. They would support that. So I have not quite totally given up on that idea, but there may be others.

RETIREMENT OF CHIMPANZEES

Dr. Collins, I have one other question I want to ask sort of off of what we have been talking about here, but it is one that I hear a lot of about, people keep asking me about. There is a great interest in this country about what is happening to our chimpanzees. As you know, we have had a great partnership with you, with the Humane Society, on retiring these chimpanzees from research.

I know Senator Landrieu has been kind of in the forefront of this, and I know she wants me to also ask this question. I was one of three Senators who requested the IOM (Institute of Medicine) report that revealed that chimpanzee research could not be justified except for a very few conditions. Again, Dr. Collins, you are to be commended for adopting the IOM recommendations so promptly, the very day the report was released. Your decision to retire approximately 310 of the 360 Government-owned chimpanzees currently in laboratories was a bold maneuver, and I thank you for that.

As a long-time appropriator, however, I know that the work takes far longer than the issuing of a policy or the signing of a bill. I am keenly aware of the complexity of creating sanctuary space, grouping, transporting chimpanzees, arranging for their care. Many of these chimpanzees suffer from illnesses and conditions we gave them for the sake of research. So could you please update the subcommittee on the plan for retiring these chimpanzees? Can you highlight the challenges and considerations involved, including any funding challenges that we need to be cognizant of?

Dr. COLLINS. Well, thank you, Mr. Chairman, and thank you for your leadership on this issue in many steps along the way, including asking the IOM to conduct that study, which concluded that the need for chimpanzees in research had now been greatly reduced and that we could, in fact, get by just fine by keeping a small group of 50 available for emergency needs or special things where only chimpanzees could be used for research.

And you also helped us with a fix on what had been a legislative problem about a cap on the amount of funds that NIH was allowed to spend on chimps in sanctuaries, and that made it possible for the retirements that we very much wanted to go forward. But you are quite right, we have a long way to go here in terms of the number of chimps that need to be moved into sanctuaries. And at the present time, that space does not exist.

We have moved many already into Chimp Haven, which is already now pretty close to capacity. We are looking vigorously at other——

Senator HARKIN. Is that the one in Louisiana?

Dr. COLLINS. Yes, and we are vigorously looking at other alternatives because there are other chimp sanctuaries to make sure that they meet the standards that you would want to see so these chimps are well cared for. And there is much interest in philanthropy in helping out with this, and the Humane Society has been a wonderful partner as well. My dear friend, Jane Goodall, who

will turn 80 years tomorrow, has been very helpful in raising the consciousness of everyone about what an important issue this is.

I would not tell you that we have this solved. I think it is going to be several years before the space can be identified, the funds can be found, and the completion of the retirements can be achieved so that we are left with just those 50 chimps for research. And we will be re-evaluating that regularly as well to see whether those are even needed at that level. But I appreciate your interest and this committee's interest in this, and we are going to keep you regularly briefed on what the needs might be.

Senator HARKIN. This started back in the late 1990s, and that is when Jane Goodall came to see us. And Senator Bingaman I know was involved. The Senator on the Senate side that introduced the bill on saving the chimps was Senator Bob Smith from New Hampshire. I remember that. I forget who the other one was, but there was a strong bipartisan effort. And so, it has taken a long time. I know we got that cap removed. It was a $30 million cap if I am not mistaken. We got that removed.

Dr. COLLINS. Yes. Yes.

Senator HARKIN. But there is a great deal of interest in moving ahead on this. And maybe if you cannot today, could you get to the committee sort of the timelines you see and what more do we need to do to kind of expedite this?

Dr. COLLINS. I am glad to do that.

[Clerk's Note: The information requested can be found in the "Additional Committee Questions" for Senator Harkin.]

Dr. COLLINS. And, Mr. Chairman, again, when I came to this job as NIH Director, I did not imagine that this issue would become so prominent. And yet it has turned out to be, I think, one of the more gratifying opportunities to work across many different constituencies and do the right thing for these special animals, who are our closest relatives.

Senator HARKIN. Our closest cousins.

Dr. COLLINS. Absolutely.

Senator HARKIN. Thank you very much.

Senator Moran.

DISEASE FUNDING PRIORITIZATION

Senator MORAN. Chairman, again, thank you. Dr. Collins, I am going to ask one more question about prioritization, and then a couple of questions for a couple of your directors.

What are the criteria—when you say this is an ongoing conversation about how to prioritize funding within NIH among the various diseases—that you look at? Is it the likelihood of success, the next opportunity for a breakthrough? What role does it play about the cost of the disease? How many people are afflicted, what the cost of care and treatment are? Is it a more scientific exercise in trying to prioritize how to spend money correctly, or is it a broader concept that you pursue?

Dr. COLLINS. That is a great question, and it is something that we work on every day. It is a mix of all those things. Certainly the public health impact has to be a concern for us, the number of people affected, and the severity of the illness, and what it does in

terms of quality of life or premature death. Those are all factored in. But if we only thought about those things, then rare diseases would get neglected, and we have learned so much from studying rare diseases. And if it is your family, it does not matter so much to you that it is a rare disease than if it is your child who is suffering from it.

We also think about scientific opportunity because that has got to be a major reason to decide to make a push in a particular direction, that something is emerging that is possible and maybe it was not a year or two previously, and you do not want to lose the opportunity to push forward on that.

On top of that, of course, a lot of our portfolio is not top down managed, and it should not be. It comes from the insights, the ingenuity, the creativity, the bold vision of those investigators out there and the universities across this country who are remarkable in their abilities to think of things that we could not have thought of. And, we, therefore, have a very substantial fraction of our portfolio that is not targeted or directed based on anybody's idea about public health need or about scientific opportunities other than the fact that they are proposing something scientific. Those then go through a peer review process. If the idea does not measure up, it does not make it into the next tier.

I would tell you, though, that peer review, while it is critical, it is not the only part of what we do. And all of the Institute directors you see here, once we have had the peer review, look across that, and the things that are somewhere near the pay line, decide what is the highest program priority based upon the issues that I just talked about—public health need, scientific opportunity—and also is our portfolio well balanced, or do we have a big pile up of things in one area and neglect in other areas. All of that calculus folds into this every day that these institute directors and I are struggling with. And I think we do a reasonable job of it, but we are always trying to do better.

NATIONAL CANCER INSTITUTE COMMUNITY PROGRAMS

Senator MORAN. Thank you for your answer. Dr. Varmus, NCI's budget request includes information on expanding access to clinical trials for patients treated in community settings and expanding access to trials by minority and underserved populations. One of those underserved populations is rural Americans, and I was interested in knowing if you could talk about the goals of that program and how many new NCI community oncology research programs, projects you might expect to find.

Dr. VARMUS. Well, Senator, I cannot give you an exact number for that, but as you were rattling off the names suggested, you are aware that we have just amalgamated two of our community-based programs into one called NCORP for Community Oncology Research Program, in which we are paying special attention to minority populations and rural populations and trying to bring hospitals that are not in our NCI designated cancer centers into the network of organizations that organize our clinical trials and provide more patients. And indeed, many of these centers that compete particularly effectively for money to support clinical trials have been in these areas—have been producing large numbers of patients to ac-

crue them into our trials over the last several years. That is an important factor in making a decision about who will get support.

As you know, we have constraints across the board because our fiscal levels are not what they used to be, so I cannot promise you any specific number until we have fully competed and awarded those grants. But our intention is to recruit as many patients as we need to carry out a new style of clinical trial that we are encouraging; that is, trials that are based as much on the genetic damage that has driven the cancer as in the organ on which the cancer has arisen. So, there is a new style of doing trials that is more costly because it requires more preliminary testing.

And we are also under the direction from a report from the Institute of Medicine to pay our investigators a higher fee for each patient accrued to those trials, so our trials have become more costly. So our interest in expanding our trials, especially with all the new therapeutics, not just drugs, but also antibodies and immune strategies, and radiotherapy that have come our way, is difficult to meet under current conditions because we cannot simply do trials. We also have to be investing, and this is part of the prioritization question in the basic research that fuels new therapeutic approaches.

And indeed, I would just make a footnote to your question about making priority judgments about what we spend our money on by pointing to a new initiative at the NCI, despite our declining budget, that targets one particular mutant gene called RAS that is mutated in over a quarter of all cancers. So here is a major target against which, despite knowing about this target for 30 years, we have made very little progress.

So we have started what is called a hub and spoke project centered in Senator Mikulski's favorite location, Frederick, Maryland, where we have a contract program called the Frederick National Laboratory for Cancer Research. We have recruited somebody from the University of California at San Francisco to come and lead this effort, which involves grantees around the country working shoulder to shoulder with a hub of people at Frederick who are leading the charge on six specific new opportunities for advancing our understanding of cancers that are driven by RAS mutations. And this is a way to lead to new kinds of compounds that can then be tested nationwide in trials that are specifically directed to cancers that have mutations in that specific gene.

CLINICAL AND TRANSLATIONAL SCIENCE AWARDS

Senator MORAN. Doctor, thank you. My time has expired. Dr. Austin, I will submit a question in writing to you. I am interested in the recommendations by the Institute of Medicine in June of 2013 on the Clinical and Translational Science Awards, and I am interested in hearing how things are going to develop. So I look forward to having a conversation with you. Thank you.

Senator HARKIN. Thank you.

Senator Mikulski.

IMPACT OF FUNDING ON U.S. INNOVATION

Senator MIKULSKI. Thank you very much, Mr. Chairman. And I just want to say to you and to all the Institute directors and everyone who works at NIH, we are fortunate to have you. But again,

I want to come back to your longevity, which shows really your dedication, and we view it as a blessing.

I also want to just comment that we—many of us here are worried about the innovation deficit both at NIH and in others. There is an effort that is being led by Senator Durbin in this area, and to that end, we on the Appropriations Committee are going to hold a full committee hearing on innovation to make sure that budget cuts and possibilities of future sequester does not dampen our standing as a world innovation leader. Yes, we worry about the deficit, but we also worry about the innovation deficit. So, we are going to be holding that hearing on April 29. Dr. Collins will be testifying, the science advisor. We are going to be listening to NSF, DARPA, and also the Energy Secretary. So we will be doing that.

WOMEN'S HEALTH

In the short time I have because others are now here, I want to raise the issue of the Office of Women's Health, that which I referenced earlier. It has been flat funded for 3 years at $40 million. Now, what I would like to get a picture of is: What do you need to have the Office of Women's Health, number two, kind of the way we are thinking about running it because each and every one of those institutes does important work with women. So when we embarked upon our initial endeavor that I referenced with Dr. Healy, breast cancer was our preoccupation. Those rates are coming down, but lung cancer in women is high.

Dr. Gibbons could tell me that women with heart disease are now escalating, and our symptoms are different, but are early diagnoses there? We could go to Dr. Landis and we think about something like atrial fib that is there, but if you do not take your blood thinner, you could end up with a stroke and wondering where are you, et cetera. And then, of course, autoimmune is several things, one of which is lupus for which only recently the first drug—therapeutic drug in 50 years, of course, came out of Human Genome in a Maryland company. So it is across all the institutes, which was the idea why we never wanted an institute on women; we wanted an office that would work. So could you tell us really with the $40 million, how is it going, do you need more, and then how do you see this working across the institutes?

Dr. COLLINS. Thanks for the question. I very much resonate with what you are saying, and we have made a lot of progress, Senator, thanks to you and others for raising this issue to the attention of NIH 20 years ago. We have been fortunate in the Office of Research on Women's Health (ORWH) to have remarkable leaders in Vivian Pinn, who recently retired, and now Janine Clayton, who is a terrific leader for that effort who I just met with day before yesterday to go over the status of her portfolio. And she has been, as Vivian was, very effective in building partnerships across NIH to support special efforts that focus on women's health.

There are particular programs in ORWH, particularly the Specialized Centers of Research on Sex Differences, the SCORE Programs, as well as training programs that have done a good job, I think, in increasing both research on women's health and also increasing the proportion of researchers who are women. And I would

say if you look at the statistics, it looks reasonably good, but there are obviously things that we need to do better.

In fiscal year 2013, 57 percent of those enrolled in NIH clinical research trials were women—57 percent. And you know what that was 20 years ago, in phase III trials, 73 percent. So, we have really come a long way. Many of those trials are, of course, disease specific and may, therefore, be sex specific, for instance in breast cancer. But many of them as in heart disease are balanced.

What we are currently particularly concerned about is actually that this same idea has not trickled down in animal models, and there is clearly a problem in that many of the investigators who are studying models of disease are studying only males—male rats, male mice—for reasons that are not defensible. And Dr. Clayton and I are about to publish an exhortation to the community about this, and we are going to start looking very closely at grants to see whether this can be corrected because if you did not learn about those sex differences in your complete clinical, you are going to miss out on an inference that might be really important.

How much money do we need? Well, we need more money as you have heard from all of us in every area of what we are doing. I would say Dr. Clayton has been quite effective in brokering the dollars that her office has to build relationships and get a lot done, but there is a lot more we could be doing.

Senator MIKULSKI. Well, as you know, the health data on women are changing, and the recent IOM report over the last 2 years shows that mortality and morbidity among women is on the rise. Anyway, a longer topic.

Dr. COLLINS. I would love to converse further with you about this at any time. It is a passion of mine as well.

Senator MIKULSKI. Thank you.

Senator HARKIN. I just want to publicly again thank Senator Mikulski. When she first came to the Senate opened our eyes and got the NIH to do internal studies to show that women were not being included in clinical trials. So it was Senator Mikulski who really moved the ball forward on that. That has been over 20 years ago.

Senator MIKULSKI. It has been a long time.

Senator HARKIN. A long time ago. And so, we thank you for moving in the right direction.

Senator Shelby.

ANIMAL RESEARCH

Senator SHELBY. Just for the record, I want to touch on something Senator Harkin brought up, and that is the research on chimpanzees, animals, and so forth. As a kid growing up in the Birmingham area in Alabama, I tried to rescue every dog in the neighborhood. I still love dogs. I still rescue them. But my parents could only feed so many.

And I was brought to reality, but that did not change my caring about animals as all of us do. On the other hand, we are all used in research, you know. I have been used by permission in research because you gather information that helps everything. But is there a real substitute—none of us want to be cruel and inhumane to animals. You have used animals in biomedical research as you

have used us, you know, in different aspects. But is there a real substitute for that? Dr. Collins, do you want to pick up on that?

Dr. COLLINS. I will, and I appreciate your making the point that research——

Senator SHELBY. Because we all love—I love dogs still.

Dr. COLLINS. So do I.

Senator SHELBY. But I do not collect them anymore, you know.

Dr. COLLINS. And we have learned enormous amounts from the study of animals in research, and we will continue to depend heavily on those insights for advances in human medicine, no doubt about it. With the chimpanzees, the IOM basically felt that there was nothing unique that would justify the continued maintenance of hundreds of chimpanzees.

Senator SHELBY. Oh, I totally agree.

Dr. COLLINS. We could shrink this back to a small group. But your question about a substitution, I am going to ask Dr. Austin to say something about an approach to studying toxicity of drugs, which traditionally has used animals, and maybe now we have got a better way to do this.

Dr. AUSTIN. Yes, thank you for the question. So this is common saw in the translational world that the best animal model is the human. And so, what we are trying to do is move more of this work to human models, and one of them I actually have sitting right in front of me. This is a kidney, but it is a kidney on a chip, and it is populated by human kidney cells, which is a wonderful model and a much better model of testing drugs than in a rat or a chimpanzee and predicting which drugs——

Senator SHELBY. Because it is a human being which you are working on ultimately to help save, right?

Dr. AUSTIN. Right. And so, this is part of a tissue chip program, that you have probably heard about, that is developing so-called organoids. They are three-dimensional micro organs on a little micro fluidic platform, a human on a chip. To be able to represent human organs in this sort of format that will dramatically change, but we believe, both the accuracy and the speed with which this testing is done and will make animal models irrelevant, obsolete. We are not there yet. We have got a lot of work to do. And actually——

Senator SHELBY. But you are going down the right road, are you not, Dr. Austin?

Dr. AUSTIN. Yes.

Senator SHELBY. You are going down the road.

Dr. AUSTIN. Yes, absolutely.

Senator SHELBY. Well, a lot of my lawyer friends are probably glad to hear this because, you know, people have said tongue-in-cheek, "Gosh, if we run out of basic research, we could use lawyers as a surplus." I said, "Do not do that."

Thank you.

Dr. COLLINS. Well, fortunately induced pluripotent stem cells came along to save the lawyers because we have this amazing new technology, which this committee has heard about, but I just got to say it gets better every day. A skin biopsy or a blood sample from any one of you could be used to make those kidney cells on that chip by doing all of this clever manipulation that has only

come to light in the last 5 years of turning genes on or off. And that means that we could generate not just any old kidney chip, but your kidney chip, and find out whether that drug that you are going to get is going to be good for you or it is going to make your kidneys not so good.

BIG DATA TO KNOWLEDGE

Senator SHELBY. Dr. Austin referred to something that I just want to pick up on with you, Dr. Collins. The data that is collected from all of us in biomedical research willfully and knowingly will help to cure diseases and so forth. How important is that in the research field, whatever it might be, immunization, or neurological, cancer, you name it.

Dr. COLLINS. It is critical, and of course we have this challenge to both keep track of increasingly enormous databases, but also to be sure we are protecting the privacy of the individuals' data so that it is not exposed in a way that they would not have given consent for.

I am glad you raised this because NIH has just this year initiated a new program we are calling BD2K, Big Data to Knowledge. We have enormous opportunities from genomics, from imaging, from electronic health records, from everything you can think of to make insights about health and disease. Unless we focus on the problem of data itself, the sort of new science called data science, we are going to get all drowning in the data that we have produced instead of making inferences from it.

So we are putting an unprecedented amount of effort into it, and this omnibus for fiscal year 2014 has given us a nice push in that regard. We aim to ramp that up to $100 million on the big data initiatives over the next couple of years, and I hired a remarkable scientist from San Diego to lead that effort, Dr. Philip Bourne.

Senator SHELBY. Mr. Chairman, one last observation and question to Dr. Collins. You mentioned earlier about how important it was for scientific investigators to go down the right road. Sometimes you do not know you are on the right road, and sometimes you are on the wrong road and discover something else, though, do you not—that is worthwhile to mankind.

Is that a question of supervision of more investigators, or is it a question of better education correlation with what people are doing? There may be no answer to it because a lot of scientific breakthroughs have come from finding something or they did something backwards. Hey, you all know it better than I do. Do you want to comment on that?

Dr. COLLINS. Absolutely. I think you are quite right that many of the most dramatic observations that have led us to insights about life and life sciences have come in directions that nobody would have predicted were going to be the case, you know, from Pasteur on. And serendipity does sort of favor the prepared mind. But I worry that at the present time with our young scientists feeling so constrained by anxieties about support that they may be less inclined when faced with an unexpected result to think of that as an opportunity to go down a new path because of the necessary kind of need to keep pursuing something that they think is in the mainstream and more likely to get supported.

This is one of those secondary effects of a difficult budget situation that worries all of us, that creativity, that innovation, that risk taking, that sort of seeking a different pathway than you had planned to is more difficult. We are funding a certain set of grants that aim to try to make that possible. The Pioneer Awards are perhaps the best known where investigators basically get 5 years of support. And if they encounter something they did not expect, they can go after it. But many of the other grant systems are not quite so favorable for that.

Senator SHELBY. Thank you, Mr. Chairman.

Senator HARKIN. Senator Durbin.

NATIONAL INSTITUTES OF HEALTH FUNDING

Senator DURBIN. Thank you very much. Thank you for dedicating a major part of your professional life to medical research at the premiere biomedical research agency in the world. And we are proud of it, and thank you for that. I also want to acknowledge—he will have plenty of tributes paid, but when the history is written of the NIH, there will be a chapter that is entitled "The Porter-Harkin-Specter" chapter when they made a decision to move forward in a dramatic way and double the appropriation for the National Institutes of Health over a 10-year period. Tom, of all of your accomplishments, you probably created more good for the world with that undertaking, although there are lot more that would compete. So I thank you for your leadership.

Dr. Collins, when I met with many of you just a few months ago, I sat down and said where do we go next. I am not sure I can come with a straight face to Congress and say double it again. I am not sure they will do it. And we had a conversation about what it takes each year to increase an investment in research in NIH and CDC, Department of Defense, healthcare, VA health research.

And you first noted that when we fall behind the cost of living, it really ties your hands in the long term to award grants. The failure to provide a regular cost of living adjustment (COLA) to NIH, as I understand it, has cost you 22 percent in terms of your ability to award grants for research over the last 10 years.

The President's budget proposed for your agency for the next fiscal year gives you, I believe, 0.7 percent COLA. We know that the actual cost of living increase will be 1.7 percent. So built into the President's budget is a further decline, falling behind more when it comes to the actual cost of living.

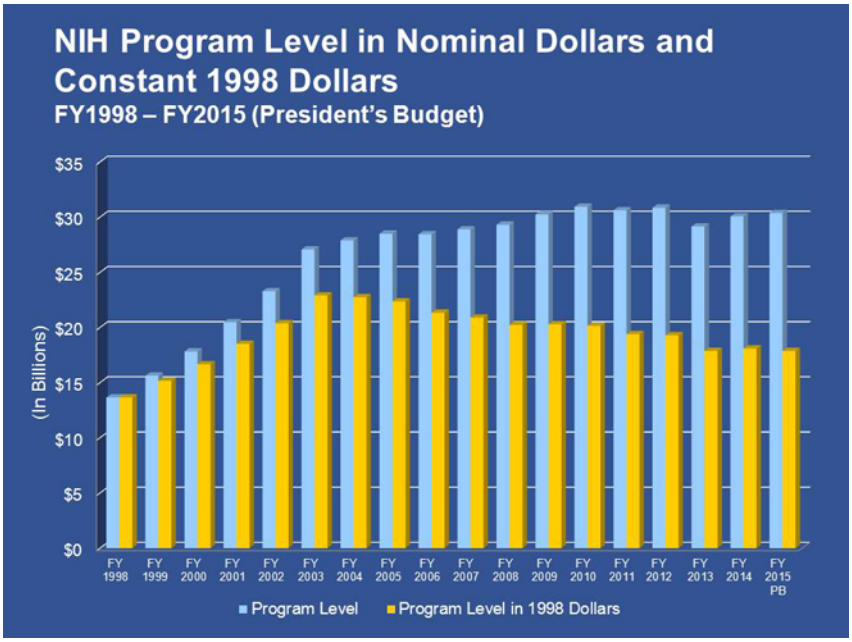
And at that time, I said, "Give me an idea of what it would take in real growth to build this agency forward." And you said—for the record I am going to ask you to comment on this—"Give us 5 percent real growth per year for 10 years over the cost of living and we will show you the kind of growth in research that America and the world needs."

So here you are on the record, and I am going to remind you of that conversation since I took it to heart and introduced a bill. So please tell me if you still believe that.

Dr. COLLINS. Senator, thank you for the question and for introducing that bill, and it was a wonderful opportunity to talk with you when you came to NIH. And your taking on this leadership is deeply appreciated.

I am showing you here this graph that I think we talked about when you came to visit, and, yes, it is exactly as you have said.

[The graphic follows:]



Dr. COLLINS. The blue bars there are the appropriations for NIH, but the yellow reflects the effect of the biomedical research and development price index (BRDPI). It is sort of like a cost of living, but it is our cost of living for doing research, the "BRDPI" as we call it. And you can see what has happened since 2003. At the end of the doubling, those yellow bars have been dipping down steadily ever since.

Earlier when you were at another hearing, I showed another version of this graph that basically says if we had stayed on the same pathway we were back in sort of 1970 to 1995, which was sort of steady growth of inflation plus about 4 percent, we would now be at about $40 billion as far as the total NIH budget, $10 billion more than what we currently have.

To get back on that pathway, which would be a wonderful way to encourage research to really move forward at the pace that it could because we are not limited by talent or by ideas. Putting this NIH trajectory on a steady path where you could count from year to year on inflation plus a percentage—and five would be wonderful—would get us back to where perhaps we really need to be in a few years, and would give such a jolt of confidence and excitement to frankly a fairly demoralized biomedical research community.

Senator DURBIN. And you have told me about it, and we know the young investigators are disappearing. Three percent are under the age of 36 today. Back 30 years ago it was 19 percent. And the other thing that struck me when we talked about AMP was you

were asking for—asked for and received a commitment of $150 million, if I remember correctly, from the top 10 pharmaceutical companies to be matched by NIH to pursue cures and whatever in the areas of Alzheimer's, type 1 diabetes, if I am not mistaken, and rheumatoid arthritis.

To put that in perspective, what I have called for in the American Cures Act is $140 billion over a 10-year period of time for the four agencies to get real 5-percent growth—$140 billion. Last year alone we spent over $200 billion in Medicare and Medicaid on Alzheimer's—$200 billion. If we could delay the onset of that disease, it would more than pay for all of the increased investment in research.

We have got to step back and take stock of what we are doing here. As we short change you, we add to the cost of our healthcare programs instead of reducing that cost. And just to put it in a global perspective, other countries are not waiting. Europe is moving forward. The United Kingdom is moving forward. In 8 years China will pass us in real dollars spent on research. And that ought to be sobering, and I hope it will awaken us.

I know the chairman has a meeting to go in a few minutes as I do, too, so I will not dwell on this other than to say I am going to keep pursuing this. I really believe that what you are doing is really a great credit to this country and will alleviate suffering and pain around the world. Thank you, Mr. Chairman.

Dr. COLLINS. Thank you, Senator.

Senator HARKIN. Thank you, Senator Durbin. Thanks for your kind words. I appreciate that.

Senator Cochran.

Senator COCHRAN. Mr. Chairman, I am pleased to join you and other members of the committee at this hearing. We appreciate your attention to the appropriations request for NIH, and we congratulate Dr. Collins and his team for the excellent work they continue to do in biomedical research, and the benefits that flow from that to our great country.

POTENTIAL CARE FOR AIDS

Last year it came to my attention that at the University of Mississippi Medical Center, a pediatrician, Dr. Hannah Gay, reported that a patient of hers who is now more than 3 years old remained HIV-free after receiving anti-retroviral therapy within hours of her birth. We have recently heard about a similar case in California. I am impressed with the research being done in my State and am hopeful that this could be good news for continued research efforts, not only in Jackson, Mississippi, but throughout the country.

What do we know or what do you know about these cases that you can share with us in terms of their impact? And what does this mean for research and treatment as far as a potential cure is concerned?

Dr. COLLINS. Well, we have the world's expert in the room, Dr. Fauci.

Dr. FAUCI. Thank you, Francis. Thank you for the question, Senator Cochran. This is truly a very important case because, as you described accurately, this was a mother who came into a clinic in Mississippi who was HIV-infected, who had no prenatal treatment

for her HIV, which put the child at very high risk. The astute physicians, pediatricians in Mississippi, instead of treating the baby in a prophylactic way to prevent infection, they immediately aggressively treated the baby as if the baby were infected. After that very rapid application of full-blown aggressive therapy as opposed to waiting for a few weeks for the diagnosis, the baby turned out actually to be infected.

By a series of circumstances after several months on therapy, there was a discontinuance in care. The mother dropped out of the healthcare system, came back several months later, and the baby had not been on therapy for several months. The physicians watched because they could not find any virus in the baby, and now 3 years out the baby is well, growing well, and has no evidence of infection, which is likely the first real cure of HIV infection.

That has now triggered an NIH-funded study in which a large number of babies who are born of high-risk mothers, namely mothers who have not been treated, will be put on aggressive therapy to see if, in fact, you can cure babies. Now, the reason that is important is that the risk to benefit ratio of treating babies aggressively very early on has weighed on the side of waiting because you are not sure if you are ever going to have the opportunity of curing someone, so you say let us not expose the baby to aggressive therapy because you might actually hurt the baby if the baby is not infected. And all you are doing is going to be saving a few weeks of treatment.

Now that you know you can actually cure a baby if you are aggressive, then the risk benefit ratio switches all the way over to the possible benefits. So it was a very important case, and it has triggered a study which will begin in the middle or end of May, a multicenter study to see if we can verify that and apply it to a larger number of babies.

Senator COCHRAN. Thank you. That is very exciting, Mr. Chairman. And I hope we learn from that that we need to listen to these witnesses when they come before our committee. We are all going to learn something, and it may be reflected in direct appropriations that really do improve not only the lives of American citizens, but actually saves their lives. Thank you very much.

CONCLUSION

Senator HARKIN. Thank you, Senator Cochran. Well, listen, thank you all very much again. It is always enlightening. Always a pleasure to hear about the National Institutes of Hope and what you are doing. I hope that our subcommittee can meet the obligations of funding that you have talked about here that is in the President's budget, maybe even go beyond that in some cases I hope in terms of funding for NIH. We just have to recommit ourselves to breaking this logjam of the funding for NIH. We have got to get back to the success rate that is less than 20 percent across the board. We have got to get down to that 15 percent level some time. I think that is what we did after we doubled it. It was down around that area, if I am not mistaken.

And so, as I said before, I think the American people support that. I do support it. And we just have to meet our obligations to do all we can to fund it and, as I said earlier, to find any ideas

on ways of funding and getting more money for NIH. We just cannot give up on this. We just cannot. Too much is at stake.

I often think there are so many young people out there with keen minds, want to get into science, biotechnology. We need to give them the hope that if they want to pursue that as a life career like so many of you have had, that they are going to have the opportunity to succeed. They are going to have the opportunity to put those keen minds to work and investigating and asking those questions of how and why and what happens.

Basic research to me has always been the most stimulating. I often put it in the past in terms of if you have—let us say you have 10 doors to a potential cure. Well, if you open one door, the odds are, what, 10 to 1, 9 to 1—I am not too good at math—that you are not going to find the right door. If you open five doors, the odds become even better, or eight or nine. That is what basic research is, is opening those doors. A lot of times it may not lead to where you think it is going to lead, but sometimes that basic research leads to something else. I always remember John—Dr. Enders and the kidney cells, and the Salk polio vaccine. That is not where he was headed, but that is what happened later on.

And so, to me basic research needs to be—we just have to fund it. It always pains me when people say, "Oh, we put all that money into basic research, but, you know, when are we going to have an end date? When are we going to find this cure and stuff?" I say, "Well, that is not a legitimate question to ask of basic research. The legitimate question to ask of basic research is do you have a question. Does something stimulate your curiosity that you are willing to spend some time to investigate it and take it as far as you can without knowing exactly what the end result is going to be?" That is what basic research is.

And we need to stimulate that kind of thinking in America, that kind of excitement about basic research. And if we do not fund NIH, we are telling young people and these keen minds do something else maybe. Maybe there is something else for you to do. So to me, the funding for NIH is not only the here and the now, but it is the next generation, the generation after that we encourage to take this up and to devote their lives to science and to basic research. We will do whatever we can to make sure that that happens.

ADDITIONAL COMMITTEE QUESTIONS

And I thank you all for all of your dedication—your lifetime dedication to exploring the frontiers of science and health, finding so many cures and therapies. It has been amazing, amazing thing to see what has happened in the last 25, 30 years that I have been here. There next 30 years can be even better. Let us make it so. Thank you very much.

I am supposed to—we will keep the record open—the record will remain open until April 9 for Senators to submit other questions and for responses to questions.

[The following questions were not asked at the hearing, but were submitted to the Department for response subsequent to the hearing:]

QUESTIONS SUBMITTED BY SENATOR TOM HARKIN

CHIMPANZEE RETIREMENT

Question. Dr. Collins, I want to thank you for the partnership you have had with this subcommittee and the Humane Society on the process of retiring chimpanzees from research. As you know, I was one of three Senators who requested the Institute of Medicine (IOM) report that revealed that chimpanzee research could not be justified except for a very few conditions. You are to be commended for adopting the IOM recommendations so promptly—the very day the report was released. Your decision to retire approximately 310 of the 360 government-owned chimpanzees currently in laboratories was suitably bold.

As a long-time appropriator, however, I know that the work takes far longer than the issuing of a policy or the signing of a bill. I am keenly aware of the complexity of creating sanctuary space, grouping and transporting chimpanzees, and arranging for their care. Many of these chimpanzees suffer from illnesses and conditions we gave them for the sake of research goals.

Can you update the subcommittee on the plan for retiring these chimpanzees? Can you highlight the challenges and considerations involved, including any funding challenges?

Answer. Thank you for your leadership in working with the National Institutes of Health (NIH) and the Institute of Medicine (IOM) to resolve issues related to NIH-owned or supported chimpanzees in research. An update on the NIH plan for chimpanzee retirement follows. Many factors must be considered to ensure a successful chimpanzee retirement process: Availability and complexity of creating the physical sanctuary space, grouping of animals based on individual and group behavioral characteristics, transporting chimpanzees (which requires healthy animals and temperate weather), and arranging for the care of an aging population. NIH has retired approximately 270 chimpanzees. At the present time, there is insufficient space in the Federal chimpanzee sanctuary system to accommodate all of the chimpanzees that will eventually be transferred. Sufficient and appropriate sanctuary space is one of the major hurdles to retiring more animals. Another is the need to select carefully the 50 most suitable research animals prior to retiring the remainder.

Since 2005, NIH has moved nearly 270 chimpanzees into the Federal Sanctuary System. Our plan to transfer all remaining NIH-owned chimpanzees from the New Iberia Research Center has been completed. The last group of nine chimpanzees was moved to the Federal Sanctuary System on June 12th. Currently, Chimp Haven, Inc. is the only facility in the Federal Sanctuary System, and it is nearing capacity. As a result of natural attrition and careful planning of group composition, we anticipate retiring approximately 30 more chimpanzees by the end of 2014. We are actively looking for alternate sites that meet, or can be modified to meet, the high standards required to ensure that these chimpanzees are well cared for. These requirements include adherence to PHS Policy on Humane Care and Use of Laboratory Animals, the CHIMP Act of 2000 (Public Law 106–551); Chimp Haven is Home Act (Public Law 110–170); the CHIMP Act Amendments of 2013 (Public Law 113–55); and the sanctuary specific regulations at 42 CFR Part 9. Chimp Haven, Inc. meets these requirements.

A Request for Information NOT–OD–14–067 (April 7, 2014) was issued to solicit information from facilities potentially qualified to join the Federal Chimpanzee Sanctuary System. Responses identified three potential options for additional sanctuary space, but all would require additional and potentially costly construction. NIH is looking at all options to develop sufficient sanctuary space but cannot yet estimate the time required.

Second, a major hurdle is the determination of the 50 chimpanzees most suitable for critical research. This selection must occur prior to retirement because the Chimp Act, as modified by the Chimp Haven is Home Act, mandates that retired chimpanzees cannot be returned to invasive research. These research chimpanzees will be chosen after an extensive NIH review of experimental protocols to ensure that all IOM criteria are met. These protocols, and the final selection of research animals, may require a period of several years. No chimpanzees will be used for NIH-supported invasive biomedical research unless chosen as part of the group of 50. Chimpanzees will stay at their current facilities, receiving high-quality medical and dental care, in their social groups, and under the care of familiar staff. Once the 50 have been chosen, remaining animals will be transferred to the Federal Sanctuary System as space permits. NIH will regularly reevaluate research needs and reduce the number of research animals as warranted.

Some chimpanzees at the research or reserve facilities will be available to move to the Federal Sanctuary System almost immediately because they will not be suitable for research protocols. The professional staff at each facility is currently identifying these animals based on many criteria. We are making progress, but it is not yet possible to specify a timeline for the disposition of all chimpanzees. It is likely to be several years before the completion of all chimpanzee retirements.

DISEASE PREVENTION

Question. I don't have to tell anyone here about my passion for disease prevention. NIH has an important role to play in conducting research on disease prevention—after all, it is the National Institutes of Health, not the National Institutes of Treatment.

I was very pleased to see that NIH recently released its first 5-year strategic plan for the Office of Disease Prevention, within the Office of the Director. How will this new plan help advance disease prevention research? I'm particularly interested in how the plan will address gaps in research that are identified by the U.S. Preventive Services Task Force.

As you know, the ACA included a provision that requires insurance companies to cover any preventive service recommended by the US Preventive Services Task Force (USPSTF) with no deductible, no co-pay. When the USPSTF review interventions, they often find that there is not enough research to make a recommendation. In those cases, they publish a number of questions that need to be answered before a recommendation could be made. NIH does not currently use these questions in their research agenda planning process.

The Office of Disease Prevention (ODP) was created in 1986 in response to the Health Research Extension Act of 1985 which required the creation of an Associate Director for Prevention. ODP includes the Office of Dietary Supplements, the Tobacco Regulatory Science Program, and supports NIH's Prevention Research Coordinating Committee.

On January 3, 2014, NIH adopted its first-ever strategic plan for disease prevention research, which had the following priorities:

—Systematically monitor NIH investments in prevention research and assess the progress and results of that research.
—Identify prevention research areas for investment or expanded effort by the NIH.
—Promote the use of the best available methods in prevention research and support the development of better methods.
—Promote collaborative prevention research projects and facilitate coordination of such projects across the NIH and with other public and private entities.
—Identify and promote the use of evidence-based interventions and promote the conduct of implementation and dissemination research in prevention.
—Increase the visibility of prevention research at the NIH and across the country.

Some examples of grants funded by ODP in 2013 are:

—Transforming Cancer Health Messaging: Engaging Alaska Native People Through Digital Storytelling
—Cyber Partners: Harnessing Group Dynamics to Boost Motivation to Exercise
—Uganda Working Group on Non-communicable Disease Risk Factors
—Psoriasis and the Risk of Diabetes
—Financial Incentives for Smoking Cessation Among Disadvantaged Pregnant Women
—Mood and Insulin Resistance in Adolescents at Risk for Diabetes
—Natural Disaster Effects on Aggressive Children and Their Caregivers
—Biomarkers in HPA Axis and Inflammatory Pathways for Suicidal Behavior in Youth
—Collaborating to Measure the Effects of Stroke Preventive Interventions

Answer. In February 2014, the NIH Office of Disease Prevention (ODP) released its first Strategic Plan which outlines the priorities that the Office will focus on over the next 5 years. The goal of this effort is to increase the scope, quality, dissemination, and impact of prevention research supported by NIH. The ODP will achieve this goal by providing leadership for the development, coordination, and implementation of prevention research in collaboration with NIH Institutes and Centers and with other partners. While the priorities and objectives outlined in the plan are designed to benefit the broader NIH prevention research community, the plan itself was developed as a tool for the ODP and does not represent a trans-NIH plan for prevention research.

The ODP strategic plan includes six strategic priorities that will allow the Office to expand its influence by, for example, providing training in prevention method-

ology and developing new strategies for identifying research needs—activities that may not otherwise be addressed by a single NIH Institute or Center but are important for advancing disease prevention research more broadly. Interest in disease prevention has grown, and NIH has a responsibility to ensure that the best prevention science is supported to inform clinical and public health initiatives at the individual, organizational, community, and policy levels. The strategic priorities included in the plan will allow the ODP to play an important role in that process while giving NIH Institutes and Centers the flexibility to support prevention research within its extramural and intramural programs that best reflects its mission and state of the science of their programs.

Strategic Priority II supports the identification of prevention research areas that may benefit from investment or expanded effort by NIH. In addition to utilizing results of new portfolio analysis tools that are under development (Strategic Priority I), the ODP will achieve this goal by working closely with the NIH Institutes and Centers, as well as other Federal and non-Federal partners such as the U.S. Preventive Services Task Force (USPSTF) to identify and prioritize gaps in prevention science and promote research in these areas to broaden the knowledge base. The USPSTF conducts scientific evidence reviews of a broad range of clinical preventive healthcare services (such as screening, counseling, and preventive medications) and develops recommendations for primary care clinicians and health systems. As part of its clinical recommendation process, the USPSTF identifies significant gaps in key areas of knowledge that may limit the full realization of the benefits of evidence-based preventive services recommendations. Of particular concern to the research community are areas that receive an Insufficient or "I" recommendation by the USPSTF, which indicates that current evidence is insufficient to assess the balance of benefits and harms of the service under consideration. As the NIH liaison to the USPSTF, the ODP refers Insufficient or "I" recommendations made by the USPSTF to NIH scientific program staff. The NIH Institutes and Centers can use this information to help them make decisions during the post peer-review process to further expand knowledge within a given research area.

To further advance Strategic Priority II, the ODP is also developing a systematic process that can be used by NIH Institutes and Centers to report recent advances or on ongoing research that addresses the research gaps identified by the USPSTF and other partners. This information, along with identified gaps, will help to highlight research areas that are in need of additional support. In addition to disseminating this information to our colleagues, the ODP will incorporate this information into its own efforts to promote collaborative prevention research projects and facilitate coordination of such projects across NIH and with other public and private entities (Strategic Priority IV).

REHABILITATION RESEARCH

Question. I was pleased to hear that NIH is implementing many of the recommendations of the 2012 Blue Ribbon panel on rehabilitation research. This is a critical area of research to improve the functions and abilities of people with severe injuries, illnesses or conditions so that they can live independently.

This research is done across many Institutes and Centers, but there is no consistent definition of rehabilitation research. Without a common definition, it is difficult to ensure that core priorities are being addressed and to accurately track the science across all of the Institutes and Centers. In the fiscal year 2012 Labor-HHS bill, this subcommittee asked that NIH adopt an NIH-wide definition. A year later, the Blue Ribbon panel went a step further to recommend that NIH adopt the WHO definition. What steps is NIH taking to address this issue?

Rehabilitation research is cross-cutting and focuses on improving the ability of people with severe injuries, illnesses, disabilities and chronic conditions to improve skills and functions and live as independently as possible.

Medical rehabilitation research is conducted at NIH through numerous Institutes and Centers. The research is intended to be coordinated by the National Center for Medical Rehabilitation Research (NCMRR) within the National Institute for Child Health and Human Development (NICHD). One of the main difficulties in coordinating the work being done at the various Centers and Institutes is that NIH does not have a consistent definition of "rehabilitation research".

The fiscal year 2012 Senate LHHS report language:

> *Rehabilitation Research.*—The Committee commends NIH for appointing a blue-ribbon panel to evaluate rehabilitation research at the National Center for Medical Rehabilitation Research [NCMRR] and across all of NIH. The Committee requests a copy of the panel's report when it is available. The panel is urged to identify gaps in the field of rehabilitation research and recommend

which ICs or other Federal agencies should be responsible for addressing them. In addition, the Committee recognizes the improvements that have been made in delineating rehabilitation research as part of NIH reporting mechanisms established since the passage of the NIH Reform Act. However, the Committee encourages NIH, through the leadership of NCMRR, to further clarify a consistent definition of rehabilitation across all institutes and centers and to seek ways to delineate between physical, cognitive, mental and substance abuse rehabilitation when characterizing NIH-supported research. Finally, the Committee encourages NCMRR to explore the broader social, emotional and behavioral context of rehabilitation, including effective interventions to increase social participation and reintegrate individuals with disabilities into their communities.

The December 2012 report from the Blue Ribbon Panel on Medicare Rehabilitation Research further emphasized the importance of taking action to clarify the definition of "rehabilitation research" by recommending the following:

"The study of mechanisms and interventions that prevent, improve, restore or replace lost, underdeveloped or deteriorating function, where function is defined at the level of impairment, activity and participation according to the WHO-ICF model (World Health Organization's International Classification of Function, Disability and Health)."

Answer. Since enactment of the 1990 law authorizing the establishment of the National Center for Medical Rehabilitation Research (NCMRR) under the auspices of the National Institutes of Health (NIH), NIH has been using the definition of medical rehabilitation research included in the statement of purpose for the Center (Sec. 452 of the Public Health Service Act, 42 U.S.C. 285g–4), which states that the purpose of the Center is to support research, training, and health information dissemination "with respect to the rehabilitation of individuals with physical disabilities resulting from diseases or disorders of the neurological, musculoskeletal, cardiovascular, pulmonary, or any other physiological system (hereafter in this section referred to as "medical rehabilitation"). This definition, which is used consistently across NIH, has allowed medical rehabilitation research to be distinguished from other rehabilitation research efforts, such as those that involve mental health or addictive disorders. The World Health Organization (WHO) definition was adopted since that time; while NIH has no objections to using the WHO definition, the law would need to be amended to replace current language.

If the definition were changed, it would need to be translated into an operational definition to allow appropriate characterization of the more than 11,000 competing grants that NIH currently funds each year. NIH uses its "Research, Condition, and Disease Categorization (RCDC)" system—a sophisticated text-data mining software—to categorize and cluster words and phrases that reflect agreed-upon definitions. See http://report.nih.gov/rcdc/. NIH has already started to develop an RCDC "fingerprint" for medical rehabilitation research, which will allow NIH to track the research portfolio as it changes over time, and to understand the breadth and depth of the portfolio as part of the upcoming effort to develop a strategic research plan.

MEDICATION IN PREGNANCY

Question. Each year more than four million women give birth in the United States and more than 3 million breastfeed their infants. Nearly all of these women will take a medication regularly or receive a vaccine, but little is known about the effect of most drugs on the woman or her child. For most drugs, we don't know the impact on child development and we don't know the impact on the effect of the medication. A study in the American Journal of Medicine illustrated that fewer than 10 percent of medications approved by the FDA since 1980 have enough information to determine their risk for birth defects. Women and doctors are forced to guess whether to continue their treatment.

This gap in understanding has become increasingly problematic as more women delay childbearing and rates of chronic disease rise. More expectant mothers than ever before are requiring medications to manage conditions such as diabetes, hypertension, depression, and asthma.

What types of research activities is NIH engaged in to fill these research gaps? What is the state of our understanding of the effect of drugs during pregnancy and breastfeeding?

Answer. Primarily through its Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB), the Eunice Kennedy Shriver National Institute of Child Health and Human Development takes a range of approaches to support research

activities on medication use in pregnancy and during breastfeeding, collaborating with other NIH Institutes and Centers as appropriate for their areas of expertise.

The Obstetric-fetal Pharmacology Research Units (OPRU) Network was established in 2004 with four academic research institutions to improve the safety and effectiveness of the medications commonly used (but often never having been tested) in women during pregnancy and postpartum. The OPRU Network has provided critical research infrastructure for a multidisciplinary collaboration of researchers to perform basic/translational studies and phase I/II clinical trials aimed at characterizing and evaluating the impact of medications on metabolism and physiological, cellular, and molecular changes during pregnancy. The OPRU Network also conducted opportunistic studies of medications in women who were already taking these medications during pregnancy. More than 100 research articles from these studies have been published in peer-reviewed scientific journals.

Some study results have directly informed clinical practice. For example, a study of the anti-diabetes drug glyburide use during pregnancy showed that glyburide can cross the placenta and that the drug's concentrations are about 50 percent lower in pregnant women with type 2 diabetes than in non-pregnant women with type 2 diabetes, suggesting that a higher dose may be needed to achieve optimal therapeutic effects. A study of oseltamivir, a medication for treating and preventing influenza, indicated that the drug plasma concentrations are much lower and apparent clearance significantly higher in pregnant women compared with non-pregnant women, suggesting an increased dose may be necessary to achieve comparable effects.

The OPRU Network currently supports a randomized clinical trial to determine the pharmacologic effects of anti-diabetic drugs (glyburide and metformin) separately, and in combination for management of gestational diabetes, a phase I clinical trial to evaluate the effect of early treatment with pravastatin for prevention of preeclampsia, and an exploratory study to identify vaginal biomarkers of response to progestin treatment of preterm birth. The Network also is funding several investigator-initiated grants on nicotine replacement therapy for smoking cessation during pregnancy and safety and effectiveness studies on anti-hypertensive medications in pregnancy. In addition, to encourage young investigators working in this area of research, the OPPTB supports several postdoctoral training programs.

CANCER AND DISTRESS

Question. I know first-hand that a cancer diagnosis can be devastating for patients and families. Studies show that half of all cancer patients experience psychological and social distress as a result of their cancer diagnosis. But there is good news: a study conducted by Dr. Barbara Andersen and published in the Journal of Oncology showed that patients with breast cancer who receive distress screening and social and emotional follow-up care have a 45 percent reduced risk of cancer recurrence, a 56 percent reduced risk of death; and a 59 percent reduction in breast cancer death even WITH recurrence.

These are remarkable outcomes. Yet the Institute of Medicine has consistently concluded that cancer care provides state of the art biomedical treatment but does little address the psychological and social needs of cancer patients.

What requirements, if any, does NCI have on its intramural and extramural research programs to screen patients for distress and ensure follow up care? What kind of research is being done, either at NCI or at the Mental Health Institute, to further this promising area of research?

Answer. As the Federal agency that supports the Nation's cancer research enterprise, the National Cancer Institute (NCI) conducts and facilitates research and the development of valid tools that can inform standard clinical practice and medical decisionmaking. However, NCI does not establish standards of care or place requirements on care-givers. Other Federal agencies and private-sector organizations (such as specialty societies and cancer-specific groups) develop medical recommendations for cancer, building upon NCI's research and the work of these other agencies in the Department of Health and Human Services (HHS) to develop guidelines or recommendations about all aspects of medical practice related to cancer care.

Still, it is important to emphasize that both NCI and the National Institute of Mental Health (NIMH) support research related to screening for emotional distress experienced by patients who receive a cancer diagnosis and subsequent treatment. In this area, NCI's role is to fund and support research that shows the efficacy and impact of systematic screening for emotional distress on cancer survivors' subsequent health and function. Historically, we have funded—and we continue to support—randomized controlled trials that test the ability of psychosocial and behavioral interventions to reduce psychological distress and promote adaptation to illness. This research has shown that a wide variety of interventions (both at the indi-

vidual and group levels and varying in content) are effective in improving understanding of illness and adherence to treatment, reducing depression, fatigue, and stress, and adopting healthy behaviors.

A key response by NCI to the Institute of Medicine (IOM) report, Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs, was to include attention to survivorship and palliative care in the funding of NCI's Community Cancer Centers pilot program (NCCCP). One of the deliverables for funded NCCCP sites was to develop the capacity to screen for distress and refer individuals to appropriate psychosocial care as needed. NCCCP sites also had to expand their psychosocial programs, as well as training of staff to identify and manage these issues in patients being treated at each institution. In addition, NCI solicited information from the clinical-investigator community about the tools they are using to screen for distress, as part of the Grid Enabled Measures (or GEM) initiative. The GEM database collects questions that measure unmet needs, depression, and anxiety. These are available for clinicians and researchers to access, evaluate, and (with the exception of copyrighted instruments) be used to care for patients under active treatment and other cancer survivors. NCI is initiating collaborations with the American Society of Clinical Oncology (ASCO) and the Commission on Cancer. In 2012, the Commission gave member sites until 2015 to implement psychosocial distress screening in their centers.

NIMH has funded several studies in recent years investigating psychological distress and depression associated with cancer diagnosis and treatment. For example, NIMH has supported the development of the Mental Health Assessment and Dynamic Referral for Oncology software, which enables oncology treatment providers to screen for and monitor several patient care domains, including: (1) mental health functioning; (2) cancer-related symptoms and side effects; (3) the patient-provider partnership; (4) barriers to treatment; and (5) adherence with medical regimen and lifestyle change recommendations. Another team of NIMH-funded researchers has studied whether depression can be prevented in patients with head and neck cancer during treatment (with relevance to other cancers), as well as whether initiating prophylactic antidepressant treatment can improve timely completion of the cancer therapy and preserve quality of life. Other NIMH-funded researchers have studied the impact of cancer treatment, as opposed to diagnosis, on mental health—for example, whether antidepressants can prevent the impact of melanoma treatment on the brain, endocrine, and immune systems.

In addition to these extramural efforts, the NIMH Division of Intramural Research Programs conducted a multiyear study investigating biological, psychological, and social factors that affect living with a chronic life-threatening illness such as cancer, HIV, or other rare diseases, as well as suicide risk and palliative care decisionmaking procedures for treating children and adolescents with life-threatening conditions.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

AMERICAN CURES ACT

Question. In 1965, the U.S. spent more than 25 percent of our non-defense discretionary budget on research and development—last year that number was 10 percent. Between 2003 and 2012, the NIH budget has not even kept up with inflation, resulting instead in a 22 percent decline in real purchasing power. The number of research grants at NIH has declined every year for the past 10 years.

Dr. Collins, you have warned that continuing this trend of funding will cause some of America's best young researchers to take their talents to other industries—or other countries.

What promising breakthroughs or developments do you think are at risk of delay due to the U.S. Federal Government failing to keep pace with inflation in funding the NIH?

Answer. NIH-supported researchers make scientific discoveries every day, advancing research related to countless health and disease issues. While it is impossible to predict exactly when breakthroughs will occur in a particular scientific field, the pace of discovery will be delayed if funding fails to keep pace with inflation. For example, this could cause delays in the significant progress that researchers are making in developing a universal flu vaccine that could offer protection against any flu virus strain, including those that may cause pandemics. Similarly, NIH efforts to develop a vaccine for HIV or even a cure for AIDS may be hampered.

In cancer research, recent results indicate that immunotherapy may be a new and effective form of treatment. However, opportunities to expand this research to in-

clude additional patients and other types of cancer may not be possible if NIH funding remains stagnant. NIH also is engaged in extensive efforts to respond to the emerging public health threat from antimicrobial resistance (AMR), including support for basic research, development of new and faster diagnostics, and creating a national database of genomic sequence data. These efforts could be hampered if NIH funding does not keep pace with inflation. NIH efforts to leverage its resources in partnerships with the private sector also could be disrupted, such as the new Accelerating Medicines Partnership (AMP) that brings biopharmaceutical companies and several nonprofit organizations together with NIH to identify and validate biological targets of disease for future drug development.

Please describe the biomedical discoveries, training of junior scientists, and economic benefits that could result if NIH was provided with a steady source of funding that increased year after year to keep up with inflation?

Answer. A steady source of funding helps support biomedical scientists. Having a budget that keeps pace with inflation would help to reassure scientists that they will have the necessary support for the duration of their projects. Steady investment in the National Institutes of Health (NIH) helps enable our researchers to achieve their full scientific potential in all research areas, fueling biomedical discoveries from autism to Alzheimer's disease to cancer to diabetes. Inflation-adjusted budgets also may enable NIH to award more grants to fund investigator-initiated research, thereby allowing the country's most innovative scientific thinkers to chart the best path forward in their research areas.

Promising young scientists who have chosen career paths outside of biomedical research in recent years due to uncertain funding also would be encouraged by a stable funding model and may reconsider pursuing research careers. Coupled with NIH's commitment to fund new investigators at success rates equal to those of established investigators, this scenario would enable NIH to attract and sustain a talented biomedical research workforce.

NIH investments reap substantial economic benefits; the agency directly supports about 300,000 researchers at more than 2,500 institutions in every state, and these investments spur additional job creation in those communities as well. In 2012, United for Medical Research estimated that NIH investments supported more than 402,000 jobs and resulted in $57.8 billion in economic output nationwide. A report from the Milken Institute indicates that a $1 increase in NIH funding can increase the bioscience industry output by $1.70 in a given year, and the long-term effects could be even greater. Given these short-term economic effects, an inflation-adjusted budget for NIH could spur job growth across the country, increase economic output, and reduce health spending by producing better, more cost-effective treatments and prevention strategies. Over the long term, increased support for NIH will lead to reductions in disease, longer lifespans, and improved quality of life for all Americans.

SEQUESTRATION AND GOVERNMENT SHUTDOWN

Question. The National Institutes of Health is the Nation's medical research agency and the leading supporter of biomedical research in the world. More than 80 percent of the NIH's budget goes to over 300,000 research personnel at more than 2,500 universities and research institutions through the United States. Last year, sequestration cut the NIH's $30.7 billion budget by almost $1.6 billion. The deleterious effects of sequestration were compounded by the government shutdown which took place October 1 to October 16 of 2013 and temporarily curtailed most of NIH's operations.

Please summarize the impact that sequestration and the government shutdown had on NIH's ability to award grants and support the training and education of scientists. Please describe the impact that sequestration and the government shutdown had on biomedical innovation and how the cuts in funding impacted patients currently enrolled in clinical trials.

Impact of Sequestration

Answer. Sequestration dampened NIH's ability to support biomedical research. The overall award rate for NIH research project grant applications in fiscal year 2013 fell to approximately 15 percent, a historic low.[1] [2] Compared to fiscal year 2012, in fiscal year 2013, NIH funded approximately 750 fewer competitive research project grants (e.g., new or renewal applications) that were determined to be highly

[1] http://nexus.od.nih.gov/all/2014/03/05/comparing-success-award-funding-rates/#sthash.aM0tN2GL.dpuf

[2] NIH's definition of "award rate" is the number of awards made in a fiscal year divided by the absolute number of applications.

meritorious in grant review, including over 200 fewer competing renewal applications. Competing renewal applications represent promising follow-on research stemming from previously funded grants. Lack of continued funding diminishes the NIH's ability to leverage previous investments and capitalize on recent scientific progress.

NIH Institutes and Centers (ICs) were also forced to reduce funding for noncompeting, ongoing research grants. Reductions varied by IC, but the NIH-wide average was −4.7 percent. Further, at least ten new funding initiatives ("request for applications" or "request for proposals" concepts) were planned but not published, including cancer studies that could have improved our ability to distinguish accurately non-lethal tumors from life-threatening ones, and autism studies to investigate genetic and environmental factors that affect the risk of autism in preterm infants.

Many of the NIH ICs also reduced their funding for training grants and fellowships. For example NIGMS, which sponsors the majority of NIH-supported pre-doctoral trainees, funded 186 fewer trainees than it would have without sequestration. Trainees who were already funded also were affected, as there was no increase in stipend levels for National Research Service Award recipients in fiscal year 2013.

Sequestration also diminished NIH's ability to conduct research at the Clinical Center. Approximately 750 fewer new patients were admitted to the NIH Clinical Center, a decrease from 10,695 new patients in 2012 to approximately 9,945 new patients in 2013. This reduced the number of patients who could have benefitted from enrollment in clinical protocols, as well as slowed the pace of important clinical research. Note that while much of the decrease in enrollment numbers is due to funding, patient recruitment is dependent on multiple factors.

Funding cuts driven by sequestration have had ripple effects throughout the biomedical research community. One recent survey examined sequestration's impact on research conducted by universities across the country.[3] The most commonly cited impacts of the sequester among survey respondents were a reduction in the number of new Federal research grants (70 percent of responding universities), delayed research projects (also 70 percent), personnel reductions (58 percent), reduced research activity (81 percent), admission of fewer graduate students (23 percent), as well as tuition reductions and reduced stipend levels for students (14 percent).

Impact of Government Shutdown

The Government shutdown impacted NIH and the biomedical research community. Approximately 75 percent of the NIH workforce was furloughed during shutdown. For the community of NIH's extramural investigators, shutdown caused delays in grant review and funding processes. Typically, NIH receives the largest number of grant applications in October. Because of the prolonged shutdown, all of the October receipt dates were rescheduled for November, including those for NIH's largest grant activities, such as the investigator initiated R01 applications, Small Grants (R03), Exploratory Development Grants (R21), AREA awards (R15), and Career Development (K) activities. Reviews of more than 11,000 grant applications were delayed by the shutdown.

October is also one of the 3 months with the largest volume of NIH Scientific Review Group meetings, the first step of peer review. Over 200 Scientific Review Group meetings had to be rescheduled due to the shutdown; most of the October meetings involved reviewers travelling to meetings scheduled to be convened "in-person". These "in-person" meetings had to be rescheduled, and travel arrangements had to be cancelled and re-arranged.

The NIH Intramural Research Program (IRP) was also profoundly affected and lost progress during the shutdown. The Clinical Center did not enroll any new patients in clinical trials or to start new trials. Therefore, approximately 200 new patients were not admitted to the Clinical Center. Of those denied access, 30 were children, including 10 with cancer. Only 15 to 20 percent of IRP staff were "excepted" from furlough, so that they could protect life (mostly in the Clinical Center, where 75 percent of the staff were required to work), guarantee safety (infrastructure support including security and the power plant), and protect large investments in materials and property (animals, cell cultures, and expensive equipment).

The shutdown took a toll on NIH intramural training programs and trainees, too. In addition to being a biomedical research enterprise, NIH is the largest training facility in the world for biomedical researchers. During the shutdown, there were approximately 4,000 postdoctoral fellows, 800 post baccalaureate students, 500 grad-

[3] Association of American Universities, Association of Public and Land-grant Universities, and The Science Coalition. Survey on Sequestration Effects: Selected Results from Private and Public Research Universities. November 2013.

uate students, and 45 medical students who were unable to conduct their research. For many of these trainees, time is of the essence. Their appointments are time-limited (less than 1 year for the medical students, up to 2 years for the post baccalaureate students, and usually three to 4 years for the postdoctoral fellows and graduate students). Loss of a few weeks of research and mentoring as well as the additional work time needed to regain momentum—while cell lines are started up again, animals are bred, and experiments that may have suffered in the shutdown are repeated—represent a significant proportion of their NIH training experience that could affect their future careers.

CONGENITAL HEART DISEASE

Question. Congenital Heart Disease (CHD) is one of the most prevalent birth defects in the United States and a leading cause of birth defect-associated infant mortality. Due to medical advancements, more people with congenital heart defects are living into adulthood.

The healthcare reform law includes a provision that authorizes the Centers for Disease Control and Prevention (CDC) to expand surveillance and track the epidemiology of CHD across the life-course, with an emphasis on adults. The Consolidated Appropriations Act of 2014 provided the CDC with $2.9 million in new funding for enhanced CHD surveillance. Recent data suggest that the number of infant deaths related to CHD is decreasing. Successful interventions in infancy and childhood are resulting in an aging population of congenital heart disease survivors.

How is the NIH systematically responding to this new population of survivors reaching adolescence, adulthood, and advanced age?

How is NIH utilizing adult congenital heart disease research experts in these efforts?

How is NIH supporting adult CHD professionals so the field can grow? Is the NIH offering training grants to grow the field? Is the Pediatric Heart Network inclusive to adult CHD experts? Is your agency formally engaging adult populations in CHD research?

Answer. Advances in diagnosis and care have led to significant improvement in survival rates for Congenital Heart Disease (CHD) such that more adults than children are now living with CHD. The National Heart, Lung and Blood Institute (NHLBI) supports research on the causes of CHD and the evolving natural history and co-morbidities in adults with CHD across the lifespan. For example, the Bench to Bassinet Program (B2B) is identifying genetic and epigenetic causes of CHD to help risk-stratify and personalize treatment for children and adults with CHD. The Pediatric Heart Network (PHN) was launched in 2001 to conduct studies to improve outcomes and quality of life in children with heart disease and includes experts in adult congenital heart disease (ACHD). The PHN is following the largest assembled cohort of individuals with single ventricle physiology into adulthood to determine barriers to transitioning to adult care and to evaluate their health status and co-morbid conditions at specific intervals. The PHN is also in the process of launching a trial in adolescents and young adults with single ventricle physiology to assess whether use of a phosphodiesterase-5-inhibitor medication will prevent functional deterioration and delay the onset of heart failure.

NHLBI also partners with ACHD-themed organizations to advance the field of ACHD research, such as The Health, Education and Access Research Trial (HEART–ACHD) and The Research Empowerment for Adult Congenital Hearts (REACH) project, both funded by NHLBI and conducted in partnership with the Adult Congenital Heart Association (ACHA) and the Alliance of Adult Research in Congenital Cardiology (AARCC). In June 2014, NHLBI and the ACHA will host a working group, "Adult Congenital Heart Disease: Emerging Research Questions," to identify critical research gaps in the care of adults with CHD. This group will build partnerships between ACHD experts and experts in the complementary fields of adult cardiovascular care and pediatric cardiology. Participants will develop methodological approaches that leverage recent progress in multicenter ACHD research and existing congenital heart disease data infrastructure, and will develop strategies to engage patients in the development and execution of research studies.

To ensure a robust community of ACHD investigators spanning basic and clinical research, NHLBI supports institutional training grants for CHD, the PHN Scholars award, to fund small pilot studies, and individual career development awards for ACHD investigators For example, an NHLBI-supported career development awardee is developing, testing, and validating a Quality Assessment Tool for Adults with Congenital Heart Disease (QAT–ACHD) for the outpatient management of selected ACHD conditions to help standardize high-quality ACHD care. Another NHLBI career development awardee is studying the role of myocardial fibrosis in three ACHD

conditions. The same investigator has also secured funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) for a pilot study on enlarged thoracic aortas in patients with bicuspid aortic valve. Mechanisms such as these are designed to ensure growing expertise in the field of ACHD research, with a strong focus on the long-term implications of CHD and its treatment for the increasing number of persons who survive for many decades after diagnosis.

QUESTIONS SUBMITTED BY SENATOR JEANNE SHAHEEN

OPPNET

Question. Can you provide an update about OppNet, the 5-year initiative to support basic behavioral and social sciences research that began in 2010? What can you tell us about the findings of that initiative? When will a report be available?

Answer. Between October 2010 and May 2014, the Basic Behavioral and Social Science Opportunity Network (OppNet) provided $64.2 million to fund 152 extramural research projects. OppNet lists all its grants by original year of funding at http://oppnet.nih.gov/resources-initiatives.asp. Among the OppNet grants is early investigator Dr. Santosh Kumar's Predicting Smoking Abstinence via Mobile Monitoring of Stress and Social Context. This study demonstrates that modern sensor technology can obtain a much more detailed and accurate representation of personal and environmental influences on smoking than previously possible. Based partially on this work, Popular Science magazine named Dr. Kumar one of the 10 most brilliant young scientists. Another project, Neural Mechanisms of Habit Formation and Maintenance, analyzes cellular, molecular, and circuit mechanisms to understand how behaviors become "automatic" regardless of outside influences. Dr. Henry Yin found that stimulating mouse neurons to generate dopamine can foster the adoption of healthy behaviors and reduce unhealthy behaviors—all without providing incentives (e.g., food rewards). These findings, already appearing in at least five peer-reviewed publications, suggest exciting possibilities for future studies with important clinical implications.

OppNet has expanded both the perspective of researchers and NIH program directors. Nineteen of OppNet's 28 new investigators (68 percent) received non-Federal funding prior to applying, compared with 21 percent of basic behavioral and social sciences research (basic-BSSR) and 39 percent of applied behavioral and social sciences research (applied-BSSR)—an example of the initiative's success at expanding NIH's scope of basic-BSSR. NIH program directors report that OppNet has increased their knowledge of other NIH Institutes and Centers (ICs)' missions and research interests and that OppNet has allowed them to solicit and fund projects that likely could not have occurred without OppNet's infrastructure. Perhaps the best examples to date are the grants funded through the funding opportunity, Basic Behavioral Research on Multisensory Processing http://oppnet.nih.gov/resources-2013fundedapp.asp. These projects explain how a combination of visual, auditory, olfactory, gustatory, non-pain somatosensory, and/or vestibular input influences basic perceptual and behavioral processes. This initiative stimulated new collaborations between ICs that were supporting research on sensory processing, but from the perspective of single sensory systems, such as vision or audition.

ICs are organized somatically or by disease. OppNet's infrastructure facilitates the trans-sensory and transdisciplinary research projects that likely would lack a clear "home." Moreover, OppNet has been so successful at coordinating basic and applied BSSR across the NIH that some ICs decided to fund all or part of 23 additional projects beyond what was planned for in the OppNet budget. As the grants funded under OppNet have not gone through a full five-year funding cycle, a formal and comprehensive program evaluation would be premature at this time. However, OppNet makes its activities and accomplishments available to the public through its Web site at http://oppnet.nih.gov/.

DIABETES

Question. I understand that, as a result of previous studies, there is evidence of a link between poor blood glucose control and development of diabetes complications, and the tremendous long-term benefits of early, effective blood glucose control, particularly in recent onset diabetes. Can you tell me what the agency is doing to better understand the underpinnings of complications like kidney disease?

Answer. Controlling and preventing diabetes are the best approaches to preventing or minimizing its many health complications, including kidney disease. Diabetes—both type 1 and type 2—is the major cause of end-stage kidney failure. The

landmark NIH-supported Diabetes Control and Complications Trial (DCCT) and its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), demonstrated how critically important it is to control blood glucose levels early in the course of type 1 diabetes in order to reduce the likelihood of subsequent complications. DCCT participants who intensively controlled their blood glucose levels had significantly lower rates of eye, nerve, kidney, and cardiovascular complications than those who received standard care. This effect extended for many years after the study ended.

A second landmark NIH-supported clinical trial, the Diabetes Prevention Program (DPP), showed that an intensive lifestyle intervention designed to achieve modest weight loss through a combination of diet and exercise lowered type 2 diabetes rates by 58 percent, and that the generic diabetes medication metformin reduced diabetes rates by 31 percent, relative to placebo. A follow-up study to the DPP, the DPP Outcomes Study (DPPOS), is assessing the long-term effects of interventions used in the DPP on the development of type 2 diabetes and its complications. After 10 years of follow-up, DPPOS found that the lifestyle intervention continued to dramatically reduce the development of type 2 diabetes—and consequently its complications—and also reduced cardiovascular risk factors.

Diabetes is the leading cause of kidney disease, followed by high blood pressure. Abnormally high blood glucose levels damage the kidney's filtering units, which progressively and irreversibly impairs kidney function. Thanks to NIH-supported research, scientists have made great progress in developing methods, in addition to controlling blood glucose levels, which slow the onset and progression of kidney disease in people with diabetes. Two types of drugs used to lower blood pressure, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), have proven effective in slowing the progression of kidney disease in people with diabetes or high blood pressure.

Because there is no way, at present, to restore kidney function once it is lost, NIH research focuses on early detection of kidney disease and strategies to slow or prevent the progression of disease. The Chronic Renal Insufficiency Cohort (CRIC) Study, one of the largest and longest ongoing studies of chronic kidney disease epidemiology in the United States, is examining the natural history of kidney disease as well as the broad range of illnesses experienced by people with kidney disease. NIH is supporting a study that aims to identify biomarkers that indicate a risk of progression of kidney disease. Research supported by NIH has enhanced our understanding of the origin of scar tissue that is common in many forms of kidney disease, how it can impair kidney function, and how it might be prevented or treated. A new initiative, currently in development, will address challenges associated with growing nephrons, the kidneys' basic filtering unit. NIH supports several studies that the private sector most likely would not undertake, including pilot studies of novel therapies for kidney disease.

EMERGENCY CARE

Question. The NIH recently created a new division, the Office of Emergency Care Research. Considering that in New Hampshire, and throughout the United States, there is an epidemic of narcotic prescription abuse and overdose deaths, what can the this new office do to help emergency providers curtail excess narcotic prescribing? How can we increase awareness among providers to decrease medically unnecessary narcotic prescriptions?

Answer. The Office of Emergency Care Research (OECR) was established in 2012 to coordinate and develop emergency care research across the National Institutes of Health. Emergency departments (EDs) are unique treatment settings in that they serve some patient populations that have little or no access to medical care, and who have few available resources. For example, EDs may be the only facilities at which poor and underserved populations receive care. For substance-using populations, they provide a unique opportunity to assess the overall health needs of the patient and link them to the care and the support required to meet all of their health needs. OECR and the National Institute on Drug Abuse (NIDA) are concerned about the epidemic of narcotic abuse and are aware of the role of the emergency care system in reducing this abuse.

NIDA is investing in research to develop clinical interventions tailored to the ED setting. The goals of these interventions are to facilitate accurate diagnoses and linkage to long-term care programs to protect the overall health of the individual. Halting accidental or unnecessary opioid prescriptions is a key component to thwarting the devastating rise in opioid overdoses. For this reason, NIDA is supporting research that will increase ED physician knowledge when treating opioid patients by:

—identifying ways to effectively implement the use of prescription drug monitoring programs (PDMPs) within the ED to decrease prescription opioid prescribing, overdoses, and deaths. Widespread use of PDMPs will provide ED physicians with the information they need to prescribe opioids to those patients who would benefit most from these essential medications, while preventing these medications from reaching populations for which they are not intended. (For more details see NIH grant 1R01DA036522–01.)

—developing improved, non-invasive devices that can detect traces of narcotics and alcohol. This will help ED physicians to diagnose and treat patients with substance abuse issues, because an accurate diagnosis of substance abuse is the first step to its treatment. (For more details see NIH grant 5R44DA031530–03.)

Since assuming the position of Director of OECR, Dr. Jeremy Brown has met with program officers and senior staff at NIDA to discuss strategies to increase research on drug abuse in the emergency care setting. In addition, in October 2013, OECR, CDC, and NIDA staff were scheduled to attend a special day training session on effective approaches to addressing substance abuse disorders in the Emergency Department. This conference was held as part of the annual meeting of the American College of Emergency Physicians. Although the Government shutdown prevented NIH staff from attending in person, this meeting emphasizes the way in which NIDA, OECR and professional organizations are cooperating to address the substance abuse epidemic.

Funding for research on the narcotic epidemic is provided by NIDA, and the Office of Emergency Care Research will continue to work with staff from NIDA to support and grow initiatives in this area.

ASTHMA

Question. In November Congresswoman DeLauro and I wrote to Secretary Sebelius to inquire about a provision in the National Heart, Lung, and Blood Institute's (NHLBI) 2007 Expert Panel Guidelines for the Diagnosis and Management of Asthma that recommends that physicians who treat the majority of children with asthma "determine exposures, history of symptoms in presence of exposures, and sensitivities." They make this recommendation so that "physicians can advise patients on ways to reduce exposure to allergens." While it has been many years since release of the guidelines, we are concerned that we are failing to meet this objective. I'd like your assurance that this work will remain a high priority for the NIH and that you will continue to work with all stakeholders to accelerate implementation of this laudable objective.

Answer. NHLBI's National Asthma Education and Prevention Program's (NAEPP) Guidelines Implementation Panel Report offers suggested strategies to enhance dissemination and adoption of key recommendations in the Guidelines. These strategies were offered as a list of possible activities for NAEPP member organizations and other professional, private sector, state and local government, and patient groups to consider undertaking within their respective organizations in order to improve asthma care, which many organizations have done. All programs address exposures to environmental allergens and irritants as part of the comprehensive approach to asthma necessary to achieve and maintain asthma control.

National professional societies and patient groups and local healthcare and community groups have made considerable progress in engaging primary care providers, allergists, and representatives of health plans to identify and overcome local barriers and accelerate implementation of recommendations in the Guidelines, including those relating to control of allergens. For example, the Centers for Medicare and Medicaid Services Health Care Innovation Awards Program included five awardees that address asthma; all of these programs incorporate attention to environmental allergens. The Environmental Protection Agency's (EPA) vibrant Community Network (http://www.asthmacommunitynetwork.org/) and annual EPA leadership Awards program offer outstanding examples of community organizations, clinicians, and healthcare administrators, including Medicaid service providers, across the country working together on programs that incorporate measures to control environmental asthma triggers, including allergens, into comprehensive asthma management. The Centers for Disease Control and Prevention's National Asthma Program and the NHLBI's National Asthma Control Initiative showcase tools and programs developed by state public health and local community clinics that can be adapted by other stakeholders. These tools include home-visit guides, environmental assessment checklists, and clinical pathways for assessing, treating, and monitoring all aspects of asthma care.

QUESTIONS SUBMITTED BY SENATOR JERRY MORAN

ACCELERATING MEDICINES PARTNERSHIP

Question. The Accelerating Medicines Partnership (AMP) is expected to address the "valley of death" in drug development. How much with the Partnership shorten the current drug development timeline and how much money will be saved?

If the Accelerating Medicines Partnership is successful, how will you determine what future disease and conditions will be added to the program?

Answer. The Accelerating Medicines Partnership (AMP) is a unique type of public-private partnership of the National Institutes of Health (NIH), the Food and Drug Administration (FDA), nonprofit organizations, and biopharmaceutical companies. AMP is supporting research focused on identifying and validating biological targets for new therapeutics, a process called target validation. AMP was just launched in February and is beginning with three specific pilot projects, in Alzheimer's disease, type 2 diabetes, and rheumatoid arthritis/lupus.

Over half of drugs fail in phase II and phase III clinical trials due to lack of efficacy, and improvements in the target validation process should reduce that failure rate. So while AMP may not affect the development timeline for a particular drug, it should increase the success rates of trials by increasing the chances that a particular drug will be effective. If AMP succeeds in validating a drug target for a particular disease, that could reduce drug development costs in that area, since companies should be less likely to conduct costly clinical trials with compounds that will fail in phase II or III because the targets of those compounds don't have the desired effect on the particular disease.

The AMP partners intend to consider other project ideas later this year. As in the selection of the pilot projects, the AMP partners would need to agree that there is a scientific opportunity in target validation in a particular disease area with these characteristics: the research project would be amenable to a public-private partnership with joint scientific planning and governance; data would be shared broadly and not be patented; and industry or research foundations would be willing to commit substantial financial and other support. The Foundation for the NIH has a project proposal form on its Web site at http://fnih.org/work/key-initiatives-0/accelerating-medicines-partnership to guide interested parties in developing project proposals for the AMP members to consider, and the AMP partners will also continue identifying and exploring their own areas of mutual scientific interest.

DARPA-LIKE PROGRAM

Question. I am concerned that researchers are now reluctant to take risks because of their concern that their research efforts will not be supported. How will NIH's new DARPA-like program address this concern?

The new DARPA-like Program is funded at $30 million and would support high risk, goal-driven activities aimed to achieve rapid technology development. While I support this type of research, I am concerned that the funding for the new program is coming from another program that supports exceptionally creative scientists proposing innovative and transformative research—High-Risk High-Reward Research. The High-Risk High-Reward Research program's funding is reduced by $21.8 million. If funding "maverick" science is a priority for NIH, why does the budget cut one high risk research program's funding to start a new one?

The Guardian ran a letter in March from a group of prominent researchers promoting additional funding to support scientific mavericks. The letter stated, "Agencies claiming to support blue-skies research use peer review, of course, discouraging open-ended inquiries and serious challenges to prevailing orthodoxies." In a time when budget resources are constrained, how do you balance funding for high-risk research projects with peer-reviewed science?

Answer. Scientific progress often advances by building incrementally upon a strong foundation of previous research and preliminary data. However, rapid advances in progress may require approaches that foster innovation and risk taking. For certain objectives, where research teams need to be actively managed to achieve defined, high-risk goals so that new expertise can be added as initial high-risk attempts fail or as new discoveries are made, the DARPA-like Other Transaction Authority (OTA) provided to the Common Fund can be very helpful. The NIH Common Fund's Stimulating Peripheral Activity to Relieve Conditions (SPARC) program will use the OTA to support a high-risk, goal-driven endeavor to develop proof of concept for an entirely new class of neural control devices that have the potential to precisely treat a wide variety of diseases and conditions. Neuromodulation to control end-organ system function has been recognized as a potentially powerful way to treat many diseases and conditions, such as hypertension and heart failure, gastro-

intestinal disorders, diabetes, and inflammatory disorders. However, the mechanisms of action for neuromodulation therapies are poorly understood. The SPARC program will support interdisciplinary teams of investigators to deliver neural circuit maps of several organ systems, novel electrode designs, minimally invasive surgical procedures, and stimulation protocols, driven by an end goal to develop new neuromodulation therapies. The program is expected to be iterative and dynamic, with the novel technologies informing mapping efforts, and mapping results defining new technology requirements. Rapid progress in this nascent field requires high levels of innovation and risk taking as well as aggressive project management to achieve these ambitious goals and capitalize on the therapeutic promise of this emerging research area.

In addition to the SPARC program, several other initiatives within the Common Fund specifically support high-risk research. The High-Risk High-Reward program, which includes the Pioneer, New Innovator, Transformative Research, and Early Independence Awards, supports exceptionally creative scientists to undertake bold and innovative research projects in any scientific area relevant to the NIH mission. For these projects, NIH has no pre-defined objective other than to foster innovative, exceptionally high-impact research through investigator-initiated projects. Therefore, for these projects, a grant mechanism, rather than the OTA mechanism, is most useful. Although Common Fund support for the High-Risk High-Reward program decreases in fiscal year 2015, the successful track record of the High-Risk High-Reward program has moved NIH's Institutes and Centers to increase their support of these awards, providing additional funding beyond the Common Fund investment.

All NIH-supported research, including programs designed to support high-risk research, undergoes a rigorous peer-review process to identify the most scientifically meritorious projects. Programs designed to support high-risk research may emphasize different criteria during peer review compared to more traditional grant mechanisms, weighting innovation and potential impact more heavily than feasibility and preliminary data. Highly innovative "blue skies" research and peer review are not mutually exclusive. Although the specific review processes for SPARC and other OTA programs may be different from grant or contract reviews, external input will still be sought to help guide the decisionmaking process.

The question of how to balance funding for high-risk research with research that is more grounded by preliminary data is perennial, and the answer varies across the NIH as scientific opportunities and challenges vary between fields of research. However, risk tolerance is a founding principle of the NIH Common Fund so that innovative solutions to the most pressing challenges may be reached.

CLINICAL AND TRANSLATIONAL SCIENCE AWARDS

Question. How has NCATS implemented the Institute of Medicine's Clinical and Translational Science Awards (CTSA) recommendations and how do you see the program growing over the next several years?

Answer. In June 2013, the Institute of Medicine (IOM) issued a report following a review of the Clinical and Translational Science Awards (CTSA) Program. The report recommended that the National Center for Advancing Translational Sciences (NCATS) take a more active role in the program's governance and direction, formalize the evaluation processes of the program, advance innovation in education and training programs, and ensure community engagement in all phases of research.

NCATS leadership is committed to implementing the recommendations of the IOM report. As a first step, NCATS has increased the programmatic and fiscal management of the grants that support this program and streamlined the way the consortium is governed, consulting closely with the CTSA Principal Investigators (PIs). For example, we have appointed a new steering committee that includes 12 CTSA PIs with staggered terms to replace the previous 90-member group.

In parallel, NCATS assembled a Working Group of its Advisory Council to provide advice on measurable objectives for the CTSA program. The group was tasked with developing clear, measurable goals and objectives for the program that address critical issues across the full spectrum of clinical and translational research (i.e. "what does success look like?"). The Working Group presented its report (http://www.ncats.nih.gov/files/CTSA-IOM-WG-Draft-Report.pdf) at the NCATS Advisory Council meeting in May. Its report addressed four of the seven recommendations in the IOM report and focused on: (1) translational workforce development, (2) engagement and collaboration with patients and communities, (3) integration of translational science across its multiple phases and disciplines within complex populations and across the individual lifespan, and (4) systemic improvements in meth-

ods and processes of translation. The measurable goals and outcomes in this report are serving as a guide for NCATS as it moves forward in developing and implementing strategies to strengthen the CTSA program and for measuring progress.

NCATS recently announced the selection of Petra Kaufmann, M.D., M.Sc., to head the NCATS Division of Clinical Innovation, which includes the CTSA program. Dr. Kaufmann served as Director of the Office of Clinical Research at NIH's National Institute of Neurological Disorders and Stroke (NINDS) and brings a wealth of expertise across the translational sciences spectrum.

With the appointment of a permanent Director for the program, the recommendations of the IOM report, and the results of deliberations by the Advisory Council and its working group, NCATS is poised to work closely with the CTSA community to improve the effectiveness and efficiency of the process of translation from scientific discovery through clinical research to improved health outcomes.

BRAIN RESEARCH THROUGH APPLICATION OF INNOVATIVE NEUROTECHNOLOGIES

Question. We discussed the Brain Research through Application of Innovative Neurotechnologies (BRAIN) Initiative at last year's budget hearing. This is an exciting proposal that could revolutionize the field of neuroscience and advance therapies for numerous diseases, including Alzheimer's. The subcommittee provided funding for this initiative in fiscal year 2014 and requested a report on the goals, objectives, budget, and timeline for the BRAIN Initiative. Could you elaborate on the commitment we are undertaking and provide specific details on what the 10 year budget picture may entail?

Answer. NIH charged a high-level working group of the Advisory Committee to the Director (ACD) to develop a rigorous plan for the Initiative that includes scientific milestones and budgetary projections (roster at http://www.nih.gov/science/brain/acd-roster.pdf). This working group comprised visionary leaders across neuroscience disciplines that were expertly positioned to delineate bold, yet achievable, multi-year timetables, milestones, and cost estimates. Over the last year, the working group met with the scientific community, patient advocates, and the general public to ensure its plan would be sufficiently informed by stakeholder input.

The working group delivered its final report for consideration by the ACD at its June 5–6 meeting. The scientific vision outlined in this report was unanimously supported by the Committee and subsequently endorsed by the NIH Director. In its findings, the group emphasized that the NIH efforts on the BRAIN Initiative should seek to map the circuits of the brain, measure the fluctuating patterns of electrical and chemical activity flowing within those circuits, and understand how their interplay creates our unique cognitive and behavioral capabilities. The following seven scientific goals were identified as high priorities for achieving this vision:

1. Identify and provide experimental access to the different brain cell types to determine their roles in health and disease.
2. Generate circuit diagrams that vary in resolution from synapses to the whole brain.
3. Produce a dynamic picture of the functioning brain by developing and applying improved methods for large-scale monitoring of neural activity.
4. Link brain activity to behavior with precise interventional tools that change neural circuit dynamics.
5. Produce conceptual foundations for understanding the biological basis of mental process through development of new theoretical and data analysis tools.
6. Develop innovative technologies to understand the human brain and treat its disorders; create and support integrated brain research networks.
7. Integrate new technological and conceptual approaches produces in Goals 1–6 to discover how dynamic patters of neural activity are transformed into cognition, emotion, perception, and action in health and disease.

These scientific goals will be maximized through seven core principles:

1. Pursue human studies and non-human models in parallel.
2. Cross boundaries in interdisciplinary collaborations.
3. Integrate spatial and temporal scales.
4. Establish platforms for preserving and sharing data.
5. Validate and disseminate technology.
6. Consider ethical implications of neuroscience research.
7. Create mechanisms to ensure accountability to NIH, the taxpayer, and the community of basic, translational, and clinical neuroscientists.

The first year of the BRAIN Initiative, fiscal year 2014, was seeded by a $40 million commitment from NIH. The President has requested $100 million in his fiscal year 2015 budget for the second year of the Initiative. For the remaining years, the working group suggests an investment ramping up to $400 million a year for fiscal

years 2016–2020 to focus on technology development and validation. They called for $500 million a year for years 2021–2025 to focus increasingly on the application of those technologies in an integrated fashion to make fundamental new discoveries about the brain. The working group emphasized that its cost estimates, which are provisional, assume that the budget for the BRAIN Initiative will supplement—not supplant—NIH's existing investment in the broader spectrum of basic, translational, and clinical neuroscience research.

A full copy of the report can be found at http://www.nih.gov/science/brain/2025/index.htm.

ALZHEIMER'S FUNDING

Question. Historically, NIH has opposed disease specific funding to allow research, not politics, to drive scientific funding decisions. However, this appears to cause a chicken and egg scenario. It is difficult for scientists to propose Alzheimer's research when there is not a robust funding stream to support their work, yet there is not a robust funding stream because scientists may not be proposing Alzheimer's research projects. So which comes first? The dedicated funding stream or the research ideas?

Answer. NIH develops targeted funding initiatives to address areas of scientific need and opportunity as identified by program staff in consultation with experts in the scientific community. The resulting initiatives are strategically deployed to make every dollar count by establishing priorities, setting goals that are both ambitious and realistic, and identifying the most promising opportunities for progress through careful planning, coordination, and resource allocation.

Although these targeted initiatives have enabled us to support a number of groundbreaking projects, it is important to note that the bulk of NIH's funding, in Alzheimer's disease and elsewhere, goes to investigator-initiated proposals—that is, proposals that are not developed in response to a specific funding initiative. For example, in fiscal year 2013, fewer than 10 percent of NIH's Alzheimer's-related research project grants were awarded under an Alzheimer's-specific funding opportunity announcement (FOA). The majority of Alzheimer's-related studies were either awarded under a more general neuroscience-focused FOA or an FOA in a related area, or were truly investigator-initiated studies reflecting the creativity and innovation of researchers seeking to build on scientific advances or offering new ways of thinking about the disease.

The importance of Alzheimer's disease research within the overall NIH research portfolio continues to be reflected in our strategic planning process and scientific funding initiatives. Our Alzheimer's-related funding opportunity announcements (FOAs) are carefully developed to advance the field consistent with the priorities established under the National Action Plan for Alzheimer's Disease and the 2012 Alzheimer's Disease Research Summit. In addition, in the past 5 years NIH has released over 40 FOAs directly relevant to Alzheimer's, and the response to each of these has been robust. In fact, each year we receive many more applications for meritorious research in Alzheimer's disease than we are able to fund.

Question. How do you prioritize funding for a disease when you know, as in the case of Alzheimer's disease, that the disease burden is only going to increase over the next 20 years?

Answer. Priority-setting processes at both the NIH and individual Institute levels are designed to maintain a balance among a wide array of diverse and compelling priorities, based on close monitoring of the scientific and medical landscapes by expert program staff and outside advisors. This enables us to use our funds efficiently and effectively in order to have the optimal impact both on the scientific field and on the public health. Alzheimer's disease is one such high-priority research area. Our planning, priority-setting, and funding initiatives fully take into account the projected increase in disease burden in this area.

The NIH Director is responsible for program coordination across the NIH Institutes and Centers (ICs) and for ensuring a balanced overall research portfolio. In turn, each IC has a process for establishing research and funding priorities based on its specific mission and the long-term research goals articulated within relevant strategic plans. These priorities are reflected in the ICs' plans to distribute resources.

To ensure that these priorities are harmonized with the wider NIH mission, the NIH Director provides centralized coordination and communication across NIH. During biweekly meetings with the IC Directors, the NIH Director considers the entire biomedical research landscape and discusses with his colleagues ways that NIH can be most effective with its investments. They hear from innovative scientists

about cutting-edge results and deliberate potential new initiatives that could significantly advance the science in a particular field.

NIH receives input from many sources when setting research and funding priorities for Alzheimer's. In addition to scientific workshops, international conferences, and other interactions with the scientific community, these sources include the National Advisory Council on Aging and the Advisory Council on Alzheimer's Research, Care, and Services, established under the 2011 National Alzheimer's Project Act. In addition, input from the 2012 Alzheimer's Disease Research Summit and the 2013 workshop on Alzheimer's Disease-Related Dementias has been instrumental in facilitating the development of our Alzheimer's research agenda.

QUESTION SUBMITTED BY SENATOR THAD COCHRAN

JACKSON HEART STUDY

Question. Dr. Collins, the Jackson Heart Study, located in Jackson, Mississippi, is the largest-ever investigation of cardiovascular disease in African Americans. In the National Heart, Lung and Blood Institute's congressional budget justification for this year, one of your focuses is on preventing and pre-empting chronic heart, lung, blood and sleep disorders. Can you tell me how the Jackson Heart Study's recent collaboration with the Framingham Heart Study can be leveraged to specifically address this particular theme?

Answer. Since it began in 1998, the Jackson Heart Study (JHS) has provided extensive information on the causes of cardiovascular disease in African Americans. JHS is also one of the largest studies of the genetic factors that affect high blood pressure, heart disease, stroke, diabetes, and other diseases that disproportionately affect African Americans. A recent JHS-related paper, for example, showed that the gene APOL1, which is known to contribute to chronic kidney disease, was found to also increase risk of cardiovascular disease in African Americans. Genetic analyses such as this provide promise for targeted therapies that can pre-empt disease. In August 2013, NHLBI contracts supporting the JHS were renewed for another 5 years.

A new collaborative research relationship has been established between the American Heart Association (AHA) and the University of Mississippi and Boston University, the academic coordinating center homes of the JHS and Framingham Heart study (FHS), respectively. The AHA-led study, called the Cardiovascular Genome Phenome Study (CVGPS), will expand upon the research taking place within the Framingham and Jackson Heart studies by investing in parallel genomic and genetic analyses among other research subjects, expanding diversity and enhancing new approaches to find more "personalized" treatment and prevention interventions that could pre-empt chronic cardiovascular disease and other conditions. The CVGPS will also seek to make new data available for analysis by qualified investigators.

More generally, NHLBI is taking the necessary steps to transform its epidemiology research efforts in a way that builds on emerging scientific tools and data platforms. NHLBI has established an Advisory Council Working Group on Epidemiology Research to strategically examine how to maximize the potential of our epidemiological studies by joining complementary data across cohorts such as the FHS and the JHS for new scientific investigations. Leveraging our available resources, through strategic partnerships and collaborations, offers the best hope to address critical needs that will not only improve treatment but also change the course of disease before irreversible consequences occur.

QUESTIONS SUBMITTED BY SENATOR RICHARD C. SHELBY

SCIENCE, TECHNOLOGY, ENGINEERING, AND MATHEMATICS

Question. The fiscal year 2015 budget request, once again, proposes a reorganization of science, technology, engineering, and mathematics (STEM) education. While the STEM proposal kept the Science Education Partnership Awards program at NIH, the budget proposes to eliminate four other STEM initiatives throughout the agency. What metrics were used to decide these programs should be eliminated?

Answer. The President's budget for fiscal year 2015 proposes a reorganization of all Federal Science, Technology, Engineering, and Mathematics (STEM) education programs. Consistent with the Government-wide STEM reorganization, NIH decided to phase out four of its smaller STEM programs and notified grantees of the discontinuation of future new STEM programs supported by the National Institute on

Drug Abuse (NIDA), the National Institute of Environmental Health Science (NIEHS), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Allergies and Infectious Diseases (NIAID). This decision to discontinue or eliminate these programs follows the recommendations of the Federal STEM Education 5-Year Strategic Plan (Appendix Table A6: STEM Education Funding in Millions by Agency, page 98). Consistent with the report language accompanying the Consolidated Appropriations Act, 2014 (Public Law 113–76), NIH is continuing support of the Science Education Partnership Award program and the Office of Science Education.

CLINICAL AND TRANSLATIONAL SCIENCE AWARDS

Question. Dr. Austin, can you tell me how the Clinical and Translational Science Awards (CTSA) program is helping underserved populations, for example in my home state of Alabama, and in other underserved states in the Deep South?

Answer. The University of Alabama at Birmingham (UAB) CTSA began a new program in 2010 called, "The Deep South Network for Translational Research (DSNTR)." It involves the UAB CTSA as the organizing hub, with participation of other institutions in the Deep South that do not have a CTSA including, Louisiana State University, Tulane University, Tuskegee University, University of Alabama-Tuscaloosa, University of South Alabama, and University of Mississippi Medical Center. It makes the sophisticated research capabilities of UAB available to investigators at these other institutions for use in multi-institutional collaborative research projects, especially those that focus on underserved populations. Further, in collaboration with Alabama's Historically Black Colleges and Universities, the UAB CTSA has built an extensive network for training the next generation of health disparities researchers.

The University of Arkansas Translational Research Institute (TRI) aims to translate successful healthcare research projects directly to patient care delivery regardless of where they live. The TRI partners with key community organizations across the state to facilitate research contacts and clinical care connections among rural and medically underserved populations. The TRI has leveraged and built upon Arkansas' statewide telemedicine program, in particular the Antenatal and Neonatal Guidelines, Education, and Learning System (ANGELS) program, which links obstetricians across the state to UAMS maternal-fetal medicine specialists. Its partnership with the Tri-County Rural Health Network has connected elderly and adult disabled citizens with home and community-based services as alternatives to nursing homes. Finally, a nascent partnership with the Philips County Faith Task Force has enabled development of a community-based program for rural veterans in Jefferson County to build capacity to conduct participatory research. The project's overarching goal is to establish a community-linked infrastructure that will increase minority participation in translational research intended to reduce racial and ethnic health disparities.

At the Atlanta CTSA, experts in community engagement seek out community healthcaregivers that can articulate the heath needs of the local population, especially those who face disproportionately higher health risks. The Atlanta CTSA includes Emory University, the Georgia Institute of Technology, and the Morehouse School of Medicine, which is dedicated to improving the health and well-being of individuals and communities with emphasis on the underserved urban and rural populations in Georgia. Morehouse provides leadership in developing programs that specifically address healthcare needs in the Atlanta region. Examples include "e-Healthy Strides," which partnered with Big Bethel AME Church to collect health data and transmit it to the parishioners' physicians; "i-Adapt," a program designed to provide instruction and motivation to people with diabetes to facilitate self-care; and EPICS (Educational Program to Increase Colorectal Cancer Screening), a program aimed at teaching primary healthcare teams about screening more effectively for colorectal cancer.

ACCELERATING MEDICINES PARTNERSHIP

Question. Under the new Accelerating Medicines Partnership program, rheumatoid arthritis and lupus will receive $41.6 million in research funding over 5 years, with about half of this funding coming from the NIH and half from pharmaceutical companies. I am concerned that the funding for lupus is not new NIH funds, but redirected funding from current research projects. Are you concerned that AMP is taking away from current lupus research resources as opposed to allocating additional resources towards lupus?

Will data generated as a result of the Accelerated Medicines Partnership be available to other scientists studying these diseases?

What other diseases and conditions will this program be supporting in the future?

Answer. The Accelerating Medicines Partnership (AMP) is a unique type of public-private partnership of the National Institutes of Health (NIH), the Food and Drug Administration (FDA), nonprofit organizations, and biopharmaceutical companies. AMP is supporting research focused on identifying and validating biological targets for new therapeutics, a process called target validation. AMP was just launched in February, and as noted, is beginning with three specific pilot projects, including a rheumatoid arthritis and lupus project.

The AMP program offers an exceptional opportunity to leverage NIH investments in lupus research with substantial funds and intellectual support from industry and non-profit organizations. Recognizing the need and opportunity, NIH, after consulting with the research community, released two Requests for Applications (RFAs) to implement the AMP program in lupus and rheumatoid arthritis. The RFAs will not take money away from existing lupus projects. We expect that a number of researchers studying lupus will apply and be funded through the AMP.

Because a major goal of the AMP is to generate pre-competitive, disease-specific data that will be accessible to the broad biomedical community, the program will also facilitate research by lupus investigators not funded through the AMP. AMP partners have also agreed that the research findings should not be patented.

The AMP partners intend to consider other project ideas later this year. As in the selection of the pilot projects, the AMP partners would need to agree that there is a scientific opportunity in target validation in a particular disease area with these characteristics: the research project would be amenable to a public-private partnership with joint scientific planning and governance; data would be shared broadly and not be patented; and industry or research foundations would be willing to commit substantial financial and other support. The Foundation for the NIH has a project proposal form on its Web site at http://fnih.org/work/key-initiatives-0/accelerating-medicines-partnership to guide interested parties in developing project proposals for the AMP members to consider, and the AMP partners will also continue identifying and exploring their own areas of mutual scientific interest.

QUESTION SUBMITTED BY SENATOR LINDSEY GRAHAM

BREAST CANCER SCREENING

Question. From 1990 to 2010, deaths from breast cancer decreased by 34 percent. However, in 2013, 230,000 new cases of breast cancer were diagnosed in the United States and almost 40,000 women died from breast cancer.

Recent news coverage has focused on studies that called into question the value of screening for breast cancers. Although the majority of scientific studies have corroborated the value of early detection of breast cancers through screening, these recent articles have created a less clear picture of the benefits of screening and may lead women to avoid periodic mammography, an experience some women already view as uncomfortable.

Given these current controversies, do you think the NCI should undertake a new study to clarify the benefits of screening so that women and their doctors will have a better idea of how breast cancer screening should fit into a woman's overall preventative health program?

Answer. We are aware of the growing concerns about the balance of benefits and harms associated with screening mammography. Some of these concerns have recently been outlined by the Swiss Medical Board in its recommendation to end the national Swiss breast cancer screening program (Reference: Biller-Andorno N and Juni P: N Engl J Med 2014;3760:1965–1967). The concerns fall into two categories. First, the reduction in cancer mortality by early detection of breast cancer using mammography may decline as more effective adjuvant chemotherapy has been developed for treatment of early- and mid-stages of breast cancer. (Much of this unequivocal progress in treatment came from NCI-sponsored randomized trials of adjuvant therapy.) Nearly all of the randomized trials testing the efficacy of mammography were conducted decades ago, in the pre-adjuvant therapy era. A recently reported and widely publicized Canadian trial started early in the era of adjuvant therapy and showed no reduction in breast cancer mortality associated with mammography screening as opposed to screening by physical examination (Reference: Miller AB, et al.: BMJ 2014; doi: 10.1136/bmj.g366). Second, new evidence of harms associated with mammography has emerged in recent years, particularly one known as overdiagnosis—the detection of non-life threatening tumors that caused anxiety and were treated with measures that carry risks, such as surgery, radiation, and chemotherapy (Reviewed in: Pace LE and Keating NL: JAMA 2014;311:1327–1335).

The emerging evidence has led to calls for additional studies in the current modern era of breast cancer therapy that would clarify the balance of benefits and harms of breast cancer screening. The ideal or "gold standard" test would be a large randomized trial comparing screening mammography to a control group that does not receive screening mammography, but such a study would not be feasible in the United States. National surveys show that a large proportion of American women continue to get routine screening mammography, with no change in usage after the U.S. Preventive Services Task Force issued its recommendations against routine screening for women ages 40–49 and for spacing mammography for women age 50–74 from annually to every 2 years (Reference: Pace LE, et al.: Cancer 2013;119:2518–2523). Given current practice, a true control group for an optimally informative "gold standard" trial appears to be impossible.

Therefore, NCI is actively funding and planning other types of studies to learn more about the benefits and harms of breast cancer screening, and to try to maximize any benefits while limiting the harms. First, NCI is taking several approaches to improve on the benefits of mammography as currently practiced. NCI funds a multi-institutional Breast Cancer Screening Consortium, a collaborative network of seven research registries designed to track outcomes of screening mammography in the community, including recall and biopsy rates, and tumor stages at diagnosis. A goal is to explore ways to achieve optimal and reproducible mammography reading in the community. A recently developed inter-divisional NCI request for applications (RFA) will focus on studying the process of screening and subsequent therapy, with a focus on overdiagnosis, which, as noted above, often leads to inappropriate and potentially harmful treatment. This project will compare tumor biology and clinical aggressiveness with the method of detection, including breast imaging, and with the criteria used for diagnosis. The research aims to identify ways to ensure timely follow-up of abnormal findings and institution of effective therapy when necessary.

Additionally, in an effort to minimize the harms of overdiagnosis, several other methods for screening are under investigation. The Early Detection Research Network (EDRN) is studying new methods to identify the molecular "fingerprints" of screen-detected tumors with little lethal potential, so that more patients can be followed without institution of unnecessary aggressive treatments. A funding opportunity announcement (FOA) for a consortium of multidisciplinary scientists specifically focused on identification of early screen-detected "non-progressor" lesions that can be safely followed is under consideration, with breast cancer as one of the four primary areas of emphasis of the proposed consortium.

A related research area involves the study of other imaging modalities to detect breast cancer. The balance of benefits and harms of breast MRI in the general population is not known, so it is not usually considered to be suited to general screening. However, some experts have recommended it as an adjunct screening tool for women at extremely high risk of breast cancer, such as women who have high-risk inherited mutations of their BRCA 1 or 2 genes, a history of ionizing radiation treatments to the chest (administered to treat other malignancies), or a family history of breast cancer. The screening recommendations for these women include both an annual mammogram and MRI for the BRCA mutation carriers and an optional MRI or ultrasound for the rest. (An update on breast cancer screening and prevention. Cruz MS, Sarfaty M and Wender RC; Primary Care: Clinics in Office Practice Vol. 41, Issue 2, June 2014, Pages 283–306.).

FDA has approved digital breast tomosynthesis or 3–D mammography devices, which use low dose x-rays for breast cancer screening but experts do not agree on its clinical use. A few small studies have shown that adding digital breast tomosynthesis to standard mammography screening may result in a significant reduction in patients being recalled for additional testing compared to routine screening mammography alone, but more research is needed. NCI is considering potential studies to see if breast tomosynthesis can improve sensitivity and lower recall rates.

SUBCOMMITTEE RECESS

Senator HARKIN. Thank you very much.

[Whereupon, at 11:55 a.m., Wednesday, April 2, the subcommittee was recessed, to reconvene subject to the call of the Chair.]